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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1949

## ORIGINAL ARTICLES

### CLINICAL INTOXICATION WITH POTASSIUM: ITS OCCURRENCE IN SEVERE RENAL INSUFFICIENCY

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AND

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THE thought of potassium producing intoxication within the human body suggests a paradox. Why should the potassium ion, a normal ingredient of human food, a necessary constituent of many body cells and the basic radical of several useful therapeutic salts, become a toxic agent? More than 100 years ago, however, it was learned that potassium salts, when injected rapidly into a vein of an animal, could cause toxic and even fatal effects on the heart.<sup>3</sup> Arden<sup>1</sup> in 1934 also observed that after the ingestion of a very large dose of a potassium salt by a normal person, paresthesias developed in the extremities. Both these experimental findings suggested that a rapid increase of the concentration of potassium in the blood might be a factor in the development of toxic action. In 1938, Winkler, Hoff and Smith<sup>30</sup> devised and carried out fundamental injection experiments in animals, which clearly confirmed a direct relationship between a rapid rise of serum potassium and abnormal alterations in the electrocardiogram. Confirmation of a similar rela-

tion was made by Thomson<sup>26,27</sup> in 1939 in a patient suffering from Addison's disease. Thomson therefore cautioned against the administration of potassium salts in cases of Addison's disease and subsequently also advised restriction of their use in cardiac and renal disease.

In 1932 a group of us became interested in the use of potassium salts in patients in whom edema had developed during the course of Bright's disease. It soon became evident that moderately large doses of potassium salts could be ingested by many of these patients without apparent toxicity.<sup>14</sup> However, in 1939, we noted in a patient suffering from serious uremia, a correlation between a rapidly increasing concentration of potassium in blood serum and the development of distinctly abnormal changes in the electrocardiogram. In many respects these alterations in the electrocardiogram and serum concentration of potassium were comparable to the experimental results of Winkler and his associates<sup>13,30</sup> following intravenous injection of a potassium salt. Our patient died within 24 hours of the

last observations and death was attributed to cardiac standstill due to potassium intoxication.<sup>18</sup> It was significant that our patient at the time of these observations was ingesting very little food and no potassium salts. Two factors seemed to be causing the rapid rise of the concentration of potassium in the serum: (1) the continuous passage of potassium from stores in body tissues into the blood stream, and (2) decreased excretion by the kidneys.

Similar results have been observed in patients suffering from uremia by Finch and Marchand and co-workers<sup>8,9,23</sup> and by Bywaters.<sup>4</sup> In 1946 Govan and Weiseth<sup>11</sup> reported potassium intoxication in an infant who had summer diarrhea and was receiving therapeutic injections of potassium chloride. The changes in the electrocardiogram and serum concentration of potassium were very similar to those noted in cases of uremia. Fortunately, the cardiac dysfunction was not irreversible and application of remedial measures soon resulted in the infant's recovery.

The relative rarity of the development of potassium intoxication even in severe uremia led us to investigate the potassium tolerance in a series of 10 such cases.<sup>16</sup> The interesting result of the study was that in only a single case did there develop temporary alterations in the electrocardiogram which were indicative of potassium intoxication. A few patients complained of paresthesias in the extremities. On the other hand, in 1 case the curve of the serum potassium was normal. This latter result, in addition to other facts observed in cases in which uremia had developed, affords considerable evidence that at times in uremia the tissue stores of potassium may be reduced.

During a period of 7 years, October, 1939, through September, 1946, a group of us were directing the care and treatment of a considerable number of

patients who had renal disease and uremia. In a small percentage of these, in fact 13 patients, hyperpotassemia was observed.<sup>15</sup> In each patient, our studies included the degree of uremia, extent of hyperpotassemia, electrocardiographic tracings and effects of treatment. Necropsy of 10 of the patients also afforded a possible correlation between observed dysfunction and pathologic alterations in the heart.

Up to the present time, studies of potassium intoxication have been chiefly limited to its occurrence in Addison's disease and Bright's disease. Most of the reported cases of potassium toxemia and the 13 cases in the present series occurred during serious phases of renal insufficiency.<sup>22</sup> Our chief aims in this report are to stress the definitive findings of potassium toxemia, to discuss in some detail the abnormal electrocardiographic patterns and to indicate therapeutic measures that may possibly alter the toxemia.

**Methods of chemical analysis:** In the present study the concentration of urea in whole blood was determined by the method of Van Slyke and Cullen<sup>28</sup> and that of creatinine in whole blood was determined by the method of Folin.<sup>10</sup> The concentration of potassium in blood serum was determined by the method of Kramer and Tisdall<sup>21</sup> as modified by Osterberg in a majority of the patients. In our hands this modification has checked with gravimetric procedures. In a few patients the method of Hartzler was employed. The concentration of calcium in blood serum was determined by the method of Clark and Collip<sup>6</sup>.

**Clinical and chemical observations.** Our series of 13 cases included acute, subacute and chronic forms of bilateral diffuse nephritis. All our patients died and the clinical diagnosis was confirmed at necropsy in 10 cases. Uremia was always present when potassium intoxication occurred. The hyperpotassemia (the concentration of potassium being 7.7 to 10.5 milliequivalents per liter of serum) and characteristic electro-

cardiographic alterations were associated with elevation of the concentrations of urea and creatinine in the blood. These varied from 74 to 540 and from 4.1 to 31.3 mg. in 100 cc. of blood respectively (Table 1). Potassium salts were administered as diuretic agents to 3 of our patients, 2 of whom had edema, and toxic effects resulted. Small test doses of 5 gm. of potassium bicarbonate were ingested by 2 other patients. The subsequent effect of potassium was studied specifically with regard to the increase of serum potassium and possible changes in the electrocardiogram. The serum potassium increased to 8.6 to 9.5 milliequivalents per liter and in 1 patient the increase was accompanied by abnormal QRS

hands and feet of a few of our patients soon after they had ingested potassium salts. Our practice in a suspected case was to estimate the serum potassium and, if it was elevated, to obtain electrocardiographic tracings. However, in certain instances a chance electrocardiogram gave us our first evidence of intoxication. Usually the hyperkalemia and characteristic alterations in the electrocardiogram were of short duration because in our patients they usually occurred during the terminal stage of uremia. Time for instituting remedial measures was of necessity brief. Bywaters<sup>4</sup> noted in his patients suffering from the crush syndrome that the administration of glucose solution and insulin temporarily bettered the elec-

TABLE 1.—POTASSIUM INTOXICATION IN 13 CASES OF RENAL INSUFFICIENCY WITH UREMIA: CONCENTRATIONS OF CERTAIN CONSTITUENTS OF BLOOD

Diagnosis*	Patients	Age, years	Blood urea, mg. per 100 cc	Blood creatinine, mg. per 100 cc	Serum potassium, mEq per liter
Subacute glomerulonephritis	2	17	130-148	6.4	8.5-8.6
Chronic glomerulonephritis	7	20-55	150-540	4.1-31.3	7.7-10.5
Acute pyelonephritis	1	43	332	17.5	7.8
Chronic pyelonephritis	2	17-36	74-291	6.5-21.0	8.7-9.1
Chronic passive renal congestion	1	61	142	4.8	8.7

\*Pathologic diagnosis in 10 cases.

complexes in the electrocardiogram, although in neither case did any serious symptoms or clinical signs of intoxication develop. The implication is clear that the administration of potassium salts to patients who had severe renal insufficiency might be a dangerous procedure.

The detection of potassium intoxication was sometimes difficult. There were no characteristic clinical signs of toxemia in our series and potassium intoxication occurred at markedly different degrees of uremia. Finch and his associates<sup>8,9,23</sup> reported the occurrence of flaccid paralysis of the extremities in 2 of their patients. Neither this symptom nor other objective neurologic abnormalities were observed in our patients. We did, however, note the development of temporary paresthesias in the

trocardiographic pattern. Finch and Marchand<sup>8</sup> also demonstrated that the electrocardiogram characteristic of potassium intoxication could be altered and approach a normal pattern after the injection of calcium salts or of a solution of sodium chloride. But if serious renal insufficiency continued, the patterns of potassium toxemia recurred and the patient succumbed with the development of cardiac standstill. The case of the infant, reported by Gowan and Weiseth,<sup>11</sup> in which acute potassium intoxication developed, is a good example of the value of applying knowledge obtained during the terminal stage of a disease to the treatment of acute intoxication. In this instance the administration of calcium gluconate, glucose solution and a transfusion



of whole blood brought about a rapid recovery.

For some years our usual treatment of patients suffering from severe uremia consisted of rather large daily intravenous infusions of solutions containing glucose, sodium chloride, sodium bicarbonate and whole blood. Often temporary improvement followed their administration. In the light of the experience of Bywaters,<sup>4</sup> of Finch and Marchand<sup>8,9</sup> and of Govan and Weiseth,<sup>11</sup> it is reasonable to suggest that the infrequent occurrence of potassium intoxication in our patients who had uremia might be because of the use of beneficial intravenous therapy. In addition to routine intravenous medication, we studied the effects of calcium in 2 patients. The immediate result was a remarkable change in the electrocardiograms to a more normal configuration. Further studies along similar lines are contemplated.

*Electrocardiographic changes.* References have already been made to the important role that electrocardiography has played in the recognition of potassium toxicity both clinically and in the experimental laboratory. Though the potassium ion may play an important role in the membrane potentials of the myocardial fibers, it is surprising to a clinician that the electrocardiogram should be found to be such a sensitive indicator of changes in the environmental potassium of the heart. It should be emphasized that the sequence of electrocardiographic changes may be practically specific for potassium intoxication, while any one electrocardiogram of the sequence might fall into the range of normal or be only suggestive.

Unfortunately from the pharmacologic viewpoint, it has not been possible in the majority of patients with changing levels of serum potassium, to study the effect of this variable alone as, in particular, coexisting disturbances

of serum pH, serum sodium, serum calcium, serum phosphorous and carbohydrate metabolism may be present. However, it would seem that the increases of T wave voltage in normal subjects<sup>10</sup> and in some patients with renal disease following the ingestion of potassium salts<sup>16</sup> are rather pure effects. From such studies it would be reasonable to assume that the opposite electrocardiographic effect seen with low serum potassium in familial periodic paralysis would be a pure effect. On the other hand, while the hypokalemia of diabetic acidosis under treatment and the hyperkalemia of Addison's disease assuredly contribute to electrocardiographic changes, other variables are operative and the electrocardiograms may not be of the suggestively diagnostic type. In diabetic coma treated with large amounts of saline solution and insulin, cardiovascular effects may be outstanding in the pronounced hypokalemic crisis but the electrocardiographic sequences are often not characteristic.

With the development of toxic concentrations of serum potassium, the characteristic electrocardiographic changes are, in general, in the following order of appearance: (1) increased height of the T wave, with steeply ascending and descending limbs producing a T wave with narrow base and a pointed apex; (2) increased intraventricular conduction time—a QRS of increased width; (3) loss of P waves; (4) gross intraventricular conduction defects, the electrocardiogram superficially simulating bundle-branch block; (5) cardiac arrest with irregular undulating potentials of low voltage.

Figures 1 through 6 illustrate various electrocardiographic features of potassium intoxication.

Cardiac irregularities of an atypical heart block form have been recorded by Marchand and Finch<sup>23</sup> but have not

been observed in our series of cases. There is a crude correlation between the late marked electrocardiographic abnormalities and the serum potassium levels but it is not felt that any definite electrocardiographic picture may be exactly predicted at a specific serum potassium level. The serum level of other cations, particularly calcium, is important and the electrocardiograms may return toward normal after injection of calcium, the serum potassium remaining unchanged' (Fig. 5, patient R. D.). QRS widening has usually appeared before loss of the P wave, sometimes to rather a marked extent (Fig. 4, patient T. L.). Whether the disappearance of the P wave is representative of a true auricular standstill remains undetermined.

The exact significance of the markedly widened QRS needs much further study. While most of our tracings of this

type and those of others simulate the picture of a right branch block, more detailed electrocardiographic evidence will need to be collected before conclusions that such a simple block was present are justified. It may be impossible to make decisions on this matter without an endocardial or cavity potential recording, which is attended by some difficulty in patients in a very ill state. Our findings on the QT interval in hyperpotassemia are difficult to interpret because of the associated metabolic disturbances. The very long QT intervals have characteristically been associated with hypocalcemia, which relationship is a long-established one.<sup>2,5,17,29</sup> However, we have seen abnormally high systolic indexes in patients whose total serum calcium levels were normal and we tentatively hold the opinion that hyperpotassemia may

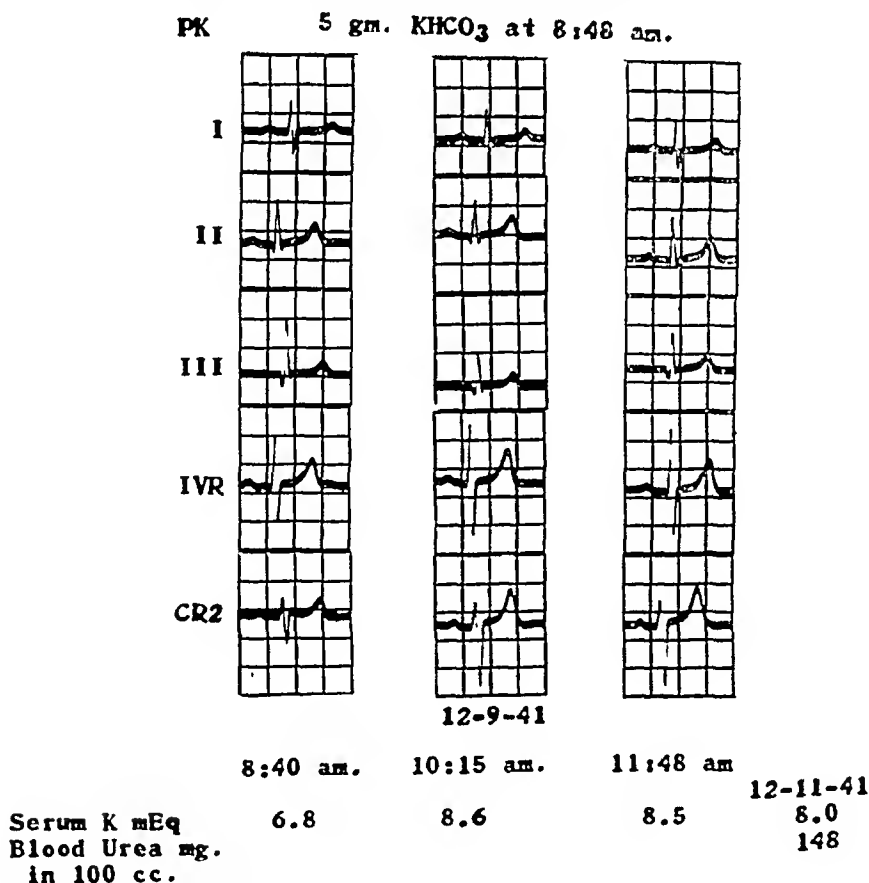


FIG. 1. P. K. Electrocardiograms taken on a man aged 17 years who had subacute glomerulonephritis and who was given 5 gm. of potassium bicarbonate.

be a factor in prolonging the QT interval.

*Pathologic observations of the heart.* Anatomic examination of the heart was made in 10 cases. The actual weights varied from a high normal, 240 gm., to a rather marked hypertrophy, 740 gm. Visible pericarditis was present in 3 cases. Coronary sclerosis was graded slight to 1 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition) in 7 cases and was graded 2 in 3 cases. In a single case there was an acute inflammatory lesion of the mitral valve. Routine his-

heart. We and others have shown that acute fibrinous pericarditis, occurring so frequently during the course of terminal uremia, gives rise to distinctly different electrocardiographic changes from those due to potassium intoxication.<sup>20,24,25</sup> It seems clear therefore that potassium can assert its toxic action on either normal or diseased cardiac tissue. Thus, our pathologic findings together with the known experimental and clinical conclusions all support a toxic action which produces a functional rather than a structural alteration in the cells of the heart.

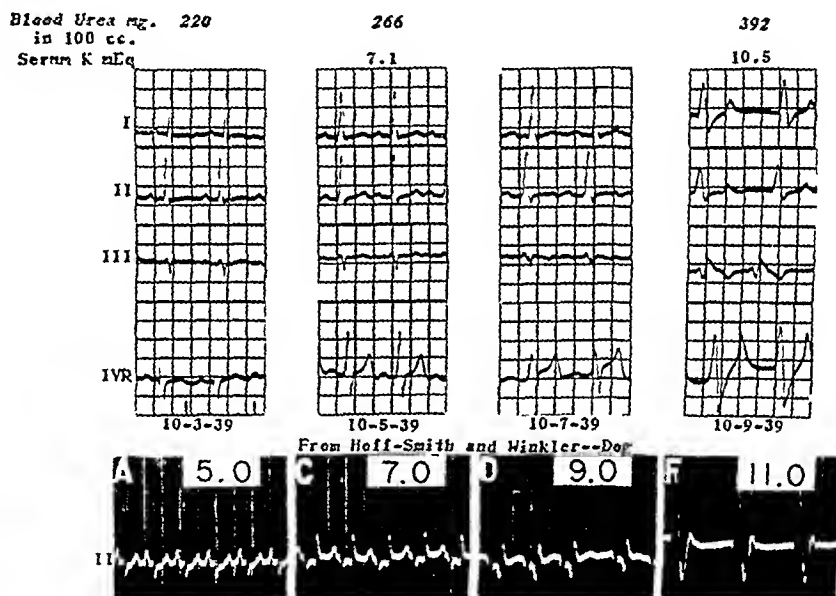


FIG. 2. B. A man, aged 21 years, who had chronic glomerulonephritis.\*

tologic study of the tissues of the hearts revealed few and as a rule only minor pathologic changes.

These rather striking variations of heart weight indicate that potassium produces its effect on the heart in a manner not closely correlated to the weight of the myocardium. The extent of sclerosis of the coronary arteries, even the most marked, grade 2, could not be interpreted as necessarily interfering with the blood supply to the

*Clinical and pathologic correlations with electrocardiographic findings.* The tracings in Figure 1 show a characteristic progressive rise of T wave voltage which, with the rise of serum potassium, has not returned to the control level after 3 hours. Necropsy was done December 27, 1941, 18 days after electrocardiographic tracings were taken. The heart weighed 400 gm. There was sclerosis graded 2 of a single branch of

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the coronary system, the left descending artery.

The man whose electrocardiograms are given in Figure 2 was the first patient whose electrocardiographic records immediately suggested to us potassium intoxication. The progressive increases of T wave voltage and of duration of QRS are illustrated. In the last tracing a marked intraventricular con-

duction defect in Figure 3 is in the normal range in spite of the high level of serum potassium and the severe uremic state, although with the knowledge of the hyperkalemia one might wonder if the QRS and T wave configurations had been altered by the high concentration of potassium in the serum. Four days later T wave negativity in prac-

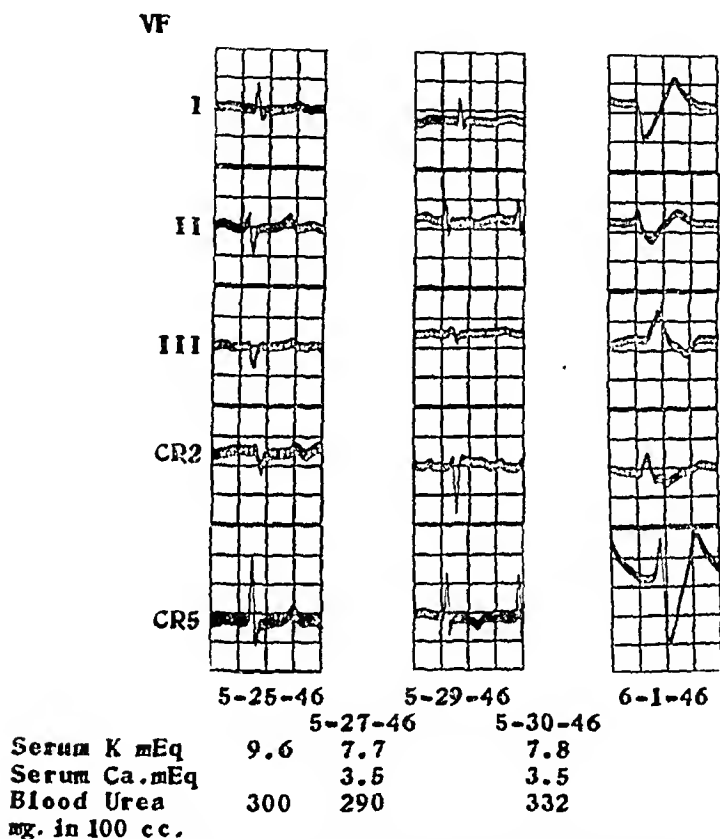


FIG. 3. V. F. A woman, aged 43 years, who had acute bilateral pyelonephritis. Electrocardiograms were taken on the patient during the fatal uremia.

duction defect and absence of P waves are to be noted. In the lower graph, electrocardiograms of animals from the paper of Hoff, Smith and Winkler<sup>13</sup> show a comparable sequence of electrocardiographic changes with increasing serum potassium levels. At necropsy in our case the heart weighed 740 gm. Definite acute fibrinous pericarditis was present. Coronary sclerosis was graded 1. The wall of the left ventricle was grossly hypertrophied.

tically all leads had appeared. The relationship of this change to the injection of a calcium salt that was given and the decrease of serum potassium is not clear. The tracing taken about 8 hours before death, however, shows a very characteristic late pattern of potassium intoxication with loss of P waves and a greatly increased duration of the QRS complex. The tracing might perhaps be interpreted as right branch block but it is deemed unlikely that

such a topical defect would be related to the hyperpotassemia. At autopsy the heart weighed 385 gm. The coronary sclerosis was graded 2. There were indications of very early pericarditis. The myocardium was normal except for a mild infiltration of the epicardial surface by plasma cells, lymphocytes and a few polymorphonuclear leukocytes

tials are to be noted and, while in these tracings they might be suspected of being secondary to the changes in the QRS deflections, they are believed to be probably primarily related to the high serum potassium levels. The intraventricular block has developed in this case at relatively low serum potassium levels and it is to be noted that it has

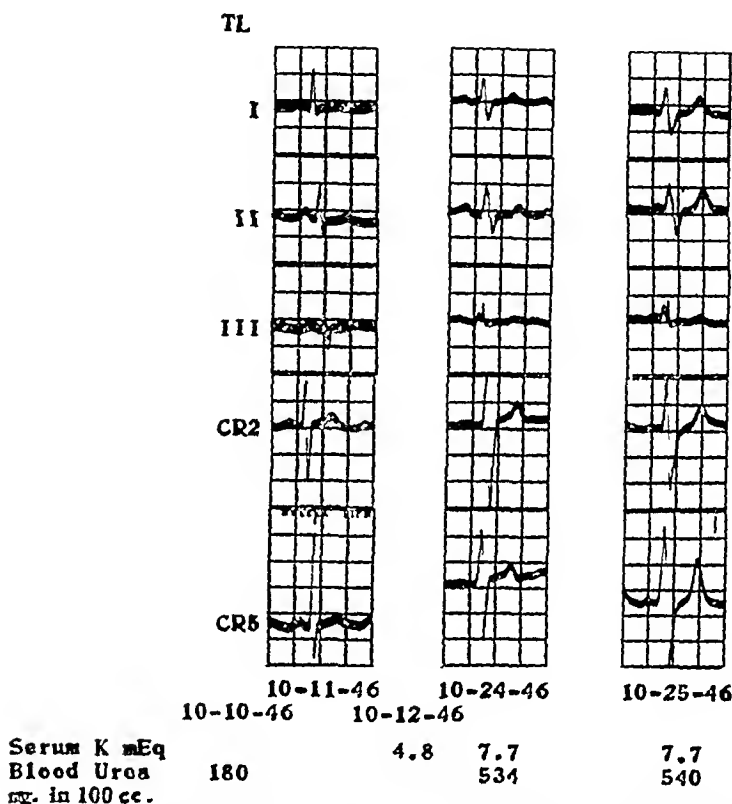


FIG. 1 T L. A man, aged 24 years, who had chronic glomerulonephritis. The 3 electrocardiograms were taken within a period of 2 weeks preceding his death with uremia

The first tracings in Figure 4 are of normal configuration. The succeeding 2 show progressive increase of the duration of the QRS, with normal sinus rhythm being retained. The intraventricular block does not conform to a typical bundle-branch pattern in the precordial leads, although the incomplete precordial exploration limits the extent of conclusions in this regard. The increased T wave poten-

progressed without further increment in serum potassium, these 2 features making the case unique in our experience. At autopsy the heart weighed 365 gm. Coronary sclerosis was graded 1 and there was some hypertrophy of the muscle of the myocardium.

The electrocardiographic tracings of the patient in the uremic state shown in Figure 5 illustrate the effect of calcium given intravenously and the re-

turn of the electrocardiogram toward normal concomitant with a decrease of serum potassium. The first tracing resembles right branch block except for the absence of an expected initial positivity of the QRS complex in the right precordial tracing. Certainly, septal infarction, which might have been sus-

markedly decreased and, except for an atypical CR-2, the tracing fits the electrocardiographic pattern commonly called left ventricular strain in our laboratories. This change occurred without any detectable change in the level of the serum potassium.

The tracings the following day still

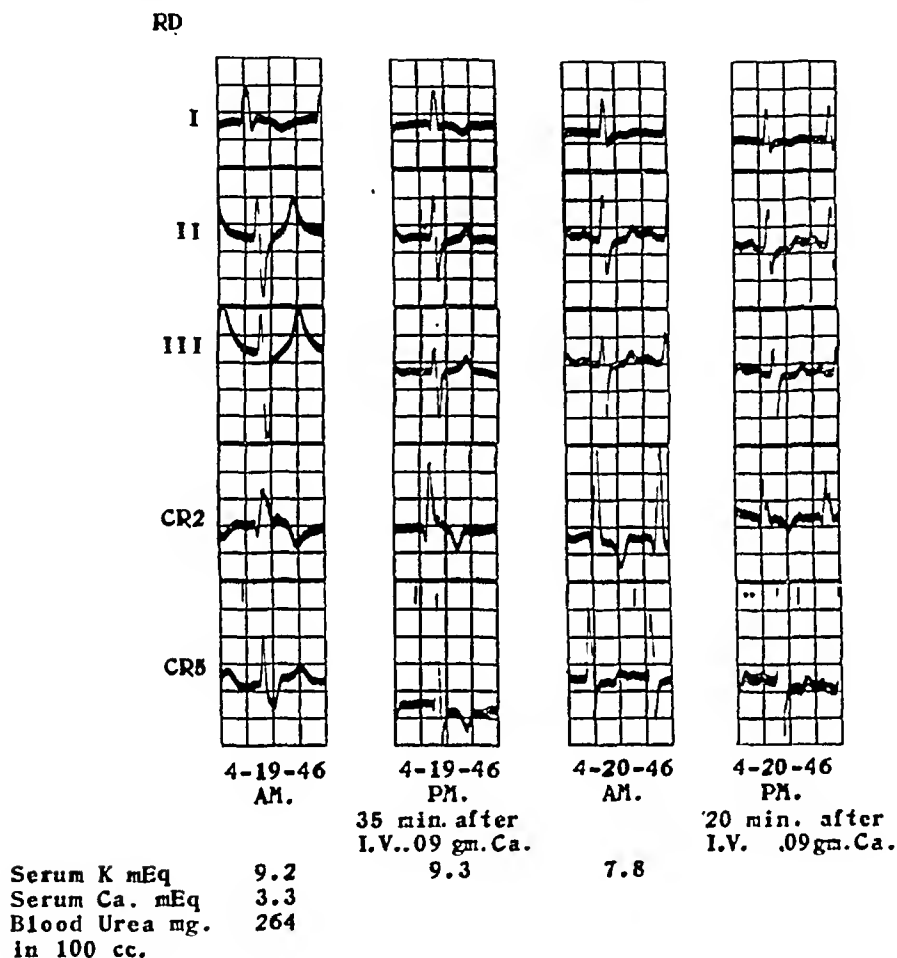


FIG. 5. R. D. A woman, aged 26 years, who had chronic glomerulonephritis.

pected in association with a right branch block, was not seen at autopsy. Additional precordial leads might have elucidated the problem in part but it is to be noted that in the subsequent tracings with decreased QRS duration there is never any gross change in the QRS configuration such as might be expected if a bundle-branch block, originally present, had disappeared.

After the intravenous administration of calcium the duration of the QRS

more closely approached normal. P waves had been restored to the records and were accompanied by a definite decrease of serum potassium. Intravenous injection of calcium at this time caused no significant alteration in the tracings.

At autopsy the heart weighed 240 gm. Coronary sclerosis was very slight, graded 1-, and the myocardium on histologic examination appeared normal.

The control tracing in Figure 6 is an essentially normal electrocardiogram. With the increase of serum potassium level there is a concomitant increase of the height of the T wave and of the length of the QRS interval (from 0.07 to 0.09 sec.). The QRS has become more biphasic and suggests the beginning of the intraventricular conduction defect which is so characteristic of the tracing in patients whose potassium concentrations approach the lethal lev-

Comment. This report confirms the previous conception that in the great majority of proved cases of potassium intoxication the patients have been suffering from severe renal insufficiency. Intoxication developed either when the intake of potassium was too great or spontaneously as an auto-intoxication. The toxemia evolves rapidly and can prove fatal by causing cardiac standstill. Thus potassium intoxication makes intelligible the fatal termination

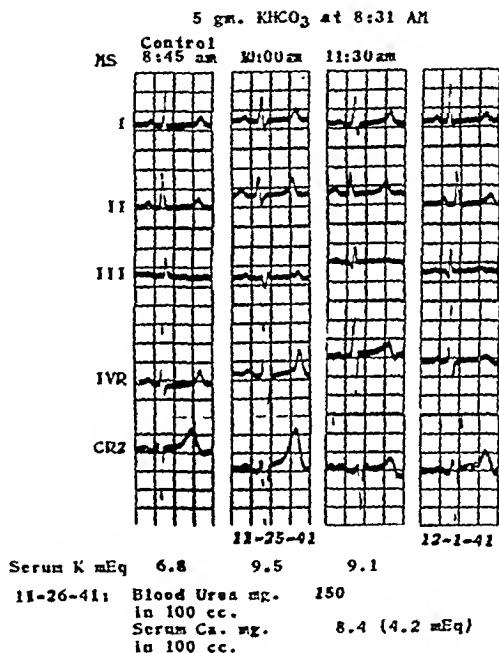


FIG. 6. M. S. Serial electrocardiograms showing the effect of increased levels of potassium in the serum.

el. Such a tracing has not been observed previously with such a small dose of potassium salt. Attention is drawn to the characteristic sharply peaked, narrow-base configuration of the T waves as seen in leads II and IV-R of the second column. The Q-T intervals are respectively 0.48, 0.48, 0.44 and 0.44 sec. and the corresponding R-R times are 1.05, 0.90, 1.10 and 1.15 sec. respectively. On November 26 the serum calcium was 8.4 mg. per 100 ml.

in a number of cases of uremia which previously baffled explanation.

The recognition of the development of potassium intoxication, whether it be due simply to a toxic intake of potassium or to a spontaneous occurrence during the course of uremia, is of importance. One should inquire into the possibility of the previous ingestion or injection of a potassium salt. Certain clinical symptoms suggest the possible presence of potassium intoxication. These are paresthesias of the hands and

feet, sudden weakness of the extremities as described by Finch and his co-workers, and shocklike syndromes. However, there are no unmistakable clinical manifestations of potassium poisoning and in their absence a potassium tolerance test may elicit valuable information. The actual proof of potassium intoxication rests on a characteristic electrocardiographic pattern and an increased concentration of potassium in the blood serum. As stated previously, in our series of cases the serum potassium varied from 7.7 to 10.5 milliequivalents per liter. The former concentration, 7.7 milliequivalents per liter, occurred in patient T. L. (Fig. 4) and is lower than previously reported, and yet the electrocardiographic changes indicated a severe disturbance in the myocardium 24 hours before death from cardiac failure.

Darrow and his co-workers<sup>7</sup> carried out an interesting series of experiments in cats which support our findings of a considerable variation in the concentration of serum potassium when toxic effects are revealed by the electrocardiogram. They also found a variable increase of the concentration of potassium in the cardiac muscle. Their results suggest that when the increase of potassium in the serum and cardiac muscles occurred rapidly, the toxic effects were more likely to result than when it was slow. Thus, the rate of entry of potassium into the myocardial cell may be an important factor in the development of the toxic effect.

The quantitative changes in the concentration of potassium in the serum or extracellular fluid are so small when compared to the large amount of intracellular potassium that on cursory investigation one might be surprised that changes in serum potassium should parallel profound physiologic disturbances. However, the changes in

the concentration of serum potassium observed in human beings have varied approximately from 2 to 10 milliequivalents per liter, actually indicating a fivefold change in serum concentration.

The difference in potassium content of cells and extracellular fluid constitutes one of the most remarkable characteristics of living tissue. This potassium gradient may be the important factor in potential differences developing in relation to all cell membranes. Certainly such potentials are readily abolished by crudely applying solutions of potassium to the epicardium and this has been a common method of producing transient injurious effects in electrocardiographic studies.

In the majority of patients with hyperpotassemia it has not been possible to study the effect of this variable alone as there are, in particular, coexisting disturbances of the serum hydrogen ion concentration, sodium and calcium. These alterations require further study and elucidation. Nevertheless, the demonstration of their presence has stimulated certain therapeutic procedures, such as the use of calcium and sodium salts and solutions of dextrose and blood, which have proved beneficial.

**Summary.** The recognition of potassium intoxication depends on the demonstration of a coexisting hyperpotassemia and a characteristic electrocardiographic sequence. The few patients in whom it has been revealed so far were suffering almost invariably from severe renal insufficiency. Potassium toxemia produces a serious condition in the myocardium, which may be reversible but also can lead to fatal cardiac standstill. Beneficial therapy can be applied and is particularly indicated in patients with early potassium intoxication.



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# EFFECT OF PARA-AMINOBENZOIC ACID ON MURINE TYPHUS A CLINICAL STUDY OF 60 CASES

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So much progress has been achieved during the past 20 years in our knowledge of the etiology, pathology, epidemiology and prevention of the rickettsioses that their control and perhaps eventual elimination now seem possible. Encouraging data related to the therapeutic value of para-aminobenzoic acid (PABA) in experimental and human infections with several types of rickettsial organisms have appeared in the literature. There is abundant experimental proof showing that para-aminobenzoic acid inhibits the growth of *R. prowazeki prowazeki* (of epidemic typhus), *R. prowazeki mooseri* (of endemic typhus), and *R. rickettsi* (of Rocky Mountain spotted fever) in chick embryos infected with these organisms.<sup>5,6</sup> Similarly an inhibitory effect has been observed in guinea-pigs infected with *R. rickettsi*<sup>1</sup> and in gerbils given multilethal doses of *R. orientalis* (of tsutsugamushi disease).<sup>7,12</sup> The drug has been found to be effective in human cases of epidemic (louse-borne) typhus,<sup>17</sup> Rocky Mountain spotted fever,<sup>8,9</sup> endemic (murine) typhus,<sup>3,10</sup> and tsutsugamushi disease.<sup>16</sup> It appears to be safe even when given in very large doses.<sup>13</sup> Its beneficial effects are thought to be due to metabolic stimulation of the cells of the host

which, by paralyzing some very poorly understood enzyme processes of the organism, inhibits their growth and multiplication.<sup>6</sup> This idea is in accord with the conclusions of Zinsser and Schoenback,<sup>18</sup> that the multiplication of intracellular rickettsiae in Maitland tissue cultures was prevented by an increase in the cellular metabolic activity, as determined by the rate of oxygen consumption.

**Material and Methods.** During the past 2 years, 60 proven cases of murine typhus were admitted to the San Juan City Hospital. The diagnostic criteria consisted in (a) a positive Weil-Felix reaction with increasing titers as the disease progressed, and reaching levels of, or higher than, 1 to 160, (b) a change from a negative to a positive complement fixation test, and (c) a clinical picture characteristic of the disease. All the diagnostic laboratory procedures reported in this paper were performed by one of us (A.P.M.) in the Bacteriology Department of the School of Tropical Medicine of San Juan, Puerto Rico.

All the patients studied were native Puerto Rican indigents from San Juan or its vicinity. Thirty-three of them received PABA, besides the other supportive measures recommended in the general management of the disease. Twenty-seven patients received only supportive treatment, thus serving as controls for the evaluation

of therapy with the drug. Of the treated cases, 23 were males and 10 females, with an average age of 26.5 years, while of the untreated, 18 were males and 9 females, with an average age of 30.6 years.

Treatment consisted in the administration of 4 gm. of PABA as an initial dose, followed by 2 gm. every 2 hours, until the temperature was normal and the patient had entered the stage of convalescence. The drug was administered in tablet form, each one containing 0.5 gm. of the medicament.\* It was very well tolerated by all the patients, no signs of toxicity being observed, apart from nausea and vomiting in 2 instances. As discussed below, we cannot feel entirely certain that the latter manifestations were provoked by the drug.

A determination of blood levels of PABA was not attempted, because of the poor results reported by others.<sup>11,14</sup> The control group was observed under conditions identical to the one under treatment. The former cases were picked at random from the whole group and received nothing but supportive therapy. All the patients studied received large amounts of intravenous 5% glucose in saline for proper hydration and adequate maintenance of nutrition and electrolyte balance. Acetyl-salicylic acid and codein sulfate were used to alleviate the headache and the general body aches when present.

A group of patients suffering from early bronchopneumonia, influenza, malaria and typhoid fever received PABA in doses ranging from 44 to 120 gm., without improvement. None of these yielded a diagnostic Weil-Felix reaction.

Most of the cases presented a fairly typical clinical picture, but the discovery of the rash was difficult among the dark-skinned subjects. The duration of the fever served as the only criterion for the duration of the disease. The disease, in the great majority of our cases, had a sudden onset with chills and fever, accompanied by headache, general body aches, photophobia and, in many instances, prostration. In the minority, the onset was preceded by prodromal symp-

toms of a few days' duration, consisting of general body aches, headache and low-grade fever. This may account for a possible error in the determination of the duration of the illness. The decrease in the severity of the symptoms, observed in all cases within 24 to 48 hours after beginning the administration of PABA, was a satisfactory index of improvement, but not of cure. The temperature was considered normal when it dropped to 99° F. or less, and continued unchanged, except for an occasional rise of very short duration and of not over 100° F., after the initial drop to normal. The latter occurred in some of the treated cases, and was commonly observed among those that did not receive the drug.

**Results.** The group treated with PABA consisted of 33 patients, and the untreated, of 27. All were proven cases of endemic (murine) typhus, by the above-set criteria. The 2 series were almost identical as regards sex, age, and race. Thus, in the treated group, the average age was 26.5 years, 2 being 50 years old, and among the controls the average age was 30.6 years, 4 being 50 years or over. In the group that received PABA 23 (70%) were males and 10 were females, while 18 (66.6%) of the control series were males and 9 females. There were 29 (88%) white and 4 colored patients in the treated group, while in the untreated 24 (89%) were white and 3 were colored. The average duration of the illness, the age, and the sex distribution of the control series very closely approached the averages reported by Stuart and Pullen<sup>15</sup> in their study of 180 untreated cases of endemic typhus. The highest temperatures were observed during the first few days of illness and averaged 104.2° F. There was a secondary rise in temperature in 21 (78%) of the 27 controls and in 10 (30.3%) of those taking PABA.

\* The drug, in the form of sodium para-aminobenzoic acid, was supplied to us by the Wyeth International Ltd. of Philadelphia, Pa., to whom we hereby express our appreciation.

TABLE 1. DATA IN 33 CASES OF MURINE TYPHUS TREATED WITH PARA-AMINOBENZOIC ACID

Case	Sex	Race	Age	Days of Fever	Day PABA Started	Days of Fever after PABA	Total of PABA in GMS	Days with PABA	Weil-Felix	Complement Fixation	Day Blood Taken
B.R.	F	W	17	12	10	2	124	5.0	1:12,800	Pos.	19
M.T.	M	W	22	10	8	2	100	4.0	1:6,400	Pos.	12
G.F.	M	W	50	11	7x	4	100	4.3	1:800	Pos.	16
J.A.R.	M	W	20	3	2	1	44	1.8	1:800	—	9
J.M.	M	C	39	12	9	3	196	8.0	1:6,400	Pos.	10
L.G.A.	M	W	34	10	7	3	219	9.0	1:1,200	Pos.	17
M.R.	M	W	50	13	9x	4	152	6.5	1:3,200	Pos.	15
R.O.	M	W	25	10	8	2	108	7.0	1:3,200	Pos.	15
P.G.	M	C	23	4	4	0	98	4.0	1:1,600	Neg.	12
M.L.B.	F	W	31	6	3	3	190	8.0	1:800	—	11
L.M.A.M.	F	W	13	4	4	0	92	3.8	1:800	Neg.	15
J.R.O.	M	W	40	8	7	1	88	3.6	1:6,400	Pos.	10
V.G.A.	M	W	18	10	8	2	152	6.3	1:3,200	—	11
M.D.T.	F	W	18	13	0	4	96	4.0	1:6,400	Pos.	18
E.P.	M	W	21	9	0°	0	136	5.7	1:3,200	—	10
M.A.F.	M	W	12	13	12	1	90	4.0	1:6,400	Pos.	13
B.V.	M	W	33	11	8	3	122	5.0	1:400	Pos.	20
J.R.	F	W	37	0	5	4	148	6.0	1:12,800	—	12
F.O.	M	W	32	12	9°	3	160	7.0	1:6,400	Pos.	14
C.R.	F	C	10	1	1	0	122	5.0	1:1,200	—	10
J.A.R.	M	W	28	5	4	1	88	3.5	1:800	—	7
A.C.	M	W	19	3	2	1	122	5.0	1:1,600	—	10
R.F.	M	C	20	10	0	4	140	5.8	1:12,800	—	10
C.L.C.	M	W	25	12	0	3	126	5.0	1:400	Pos.	14
M.T.	M	W	22	10	8	2	104	4.3	1:3,200	—	12
A.M.F.	M	W	13	14	12°	2	96	4.0	1:6,400	Pos.	15
M.A.	F	W	14	7	4	3	122	5.0	1:800	—	14
M.R.D.	F	W	34	4	4	0	74	3.0	1:200	Pos.	16
E.M.	F	W	44	9	7x	2	08	4.0	1:800	—	6
M.M.	M	W	36	7	5	2	150	0.5	1:6,400	Pos.	12
N.M.	F	W	25	12	8	4	127	5.0	1:800	—	11
P.P.	M	W	31	4	3	1	48	2.0	1:1,600	—	7
B.O.	M	W	13	8	4	4	06	4.0	1:6,400	—	17
Averages			26.5	8.7	6.5	2.2	121.4	5.0			12.8

° Received sulfadiazine.

x Received penicillin.

TABLE 2. DATA IN CONTROL GROUPS OF 27 CASES OF MURINE TYPHUS NOT TREATED WITH PARA-AMINOBENZOIC ACID

Case	Sex	Race	Age	Days of Illness on Admission	Days of Fever	Days of Fever after Admission	Weil-Felix	Day Blood Taken
W.R.R.	M	C	24	7°	17	10	1:1200	16
V.G.	M	W	55	5	14	9	1:800	10
V.B.	M	W	42	3	15	12	1:1600	15
J.G.P.	M	W	40	10	14	4	1:6400	16
M.A.	F	W	60	6	15	9	1:800	10
J.A.R.	F	W	58	5	16	11	1:3200	15
S.T.F.	F	W	40	7x	13	6	1:3200	16
R.C.S.	F	W	23	2	12	10	1:800	12
J.A.	F	W	28	8	16	8	1:6400	13
O.C.	M	W	27	6	14	8	1:1600	11
T.S.R.	M	W	22	1	14	13	1:1200	14
J.R.C.	M	W	33	10x	18	8	1:3,200	13
M.L.M.	M	W	21	4x	17	13	1:5,120	15
L.R.	F	W	16	5°	13	8	1:6,400	11
J.A.Ke.	M	C	13	8x	22	14	1:3,200	16
A.W.	M	W	26	10	15	5	1:800	15
S.C.N.	M	W	23	3°	14	11	1:1200	12
J.R.R.	M	W	20	7	16	9	1:3,200	15
P.T.	M	W	23	10°	14	4	1:3,200	11
B.N.	M	W	50	6x	17	11	1:800	8
C.M.	F	W	40	3	13	10	1:6,400	17
G.O.	M	W	15	9x	13	4	1:800	11
A.M.S.	F	W	19	2	14	12	1:400	13
I.M.P.	M	W	28	6	16	10	1:1,200	16
F.Z.	F	W	25	8°	12	4	1:400	7
G.G.M.	M	W	15	4	13	9	1:1,200	15
M.C.T.	M	W	30	12°	15	3	1:800	13
Averages			30.6	6.2	15.0	8.8		13.2

° Received sulfadiazine.

x Received penicillin.

There were no deaths in either series.

The duration of the illness before admission to the hospital was from 1 to 12 days, with an average of 6.2 days for the untreated patients. Treatment was started between the 1st and 12th day, with an average of 6.5 days, in those that received PABA. The duration of the illness after hospitalization, in the untreated group, averaged 8.8 days, while in the treated it was only

headache, body aches, prostration, constipation and photophobia within 48 hours of the initiation of treatment with PABA. The drug, however, failed to prevent the appearance of the rash, or to alter its distribution, in 12 of the cases. The rash appeared during treatment in 5 cases, and in 7, after the temperature had become normal (Table 3). Treatment was started early in the course of the disease in all these cases.

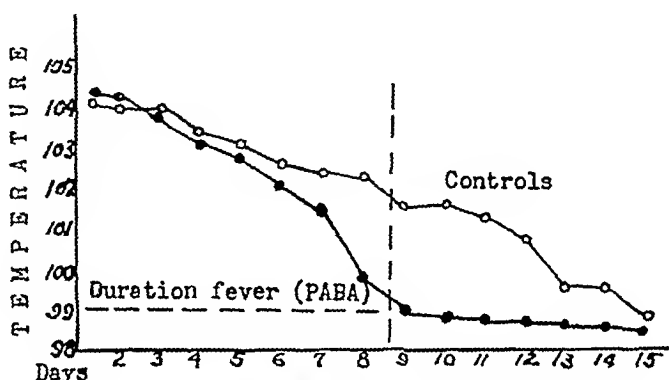


Fig. 1.—Temperature curves (averages).

TABLE 3. INCIDENCE AND TIME OF APPEARANCE OF RASH

Time of Appearance of Rash	No. of Cases	Percentage
<b>TREATED CASES</b>		
Present on Admission	12	36.4
Appeared After Therapy	7	21.2
Appeared During Therapy	5	15.1
Not Present	9	27.3
Total	33	100.0
<b>UNTREATED CASES</b>		
Present on Admission	10	37.0
Appeared after Admission	9	33.3
Not Present	8	29.7
Total	27	100.0

2.2 days. The total duration of the disease in the treated group averaged 8.7 days, as compared with 15 days among the controls. The total amount of PABA administered averaged 121.4 gm., received in 1.8 to 9 days, and in total doses that ranged from 44 to 219 gm. (A summary of the data appears in Table 1 and 2, and Fig. 1.)

In the great majority of the patients there was some improvement in the

No rash was observed in 9 of the treated and in 8 of the controls. The variability in the extent and prominence of the rash in the control series renders the observations in this respect, in the treated cases, difficult of interpretation. Nevertheless, it was noted that on receiving treatment the rash assumed a violaceous color and tended to disappear more rapidly than in the control group.

In general, the patients receiving treatment from early in the course of the disease responded better than did those in whom therapy was delayed for more than a week. Taking 12 to 18 days as the average natural duration of uncomplicated murine typhus,<sup>15</sup> we can assume that the drug failed in 9 instances. But it must be noted that in 6 patients administration of the drug was started after the 7th day of illness and yet the results were favorable. This seems to indicate that although favorable results may be obtained in the treatment of endemic typhus after the 7th day of illness, the greater efficacy of an early start of therapy should be emphasized.

As mentioned before, severe nausea and vomiting were observed in 2 of the treated patients. However, these symptoms could not be attributed exclusively to the drug, although the latter may have increased their severity, for some of the controls presented the same symptoms, before or after hospitalization. Repeated blood studies failed to reveal severe signs of toxicity during or after treatment with the drug. Although the white cell count in 3 instances was under 4,000 per c.mm. after the completion of the treatment, the differential counts were essentially normal, aside from a relative lymphocytosis of 67% in one instance. The bone-marrow was active in this case, as evidenced by an Arneth shift to the left. No changes were observed in the hemoglobin content or in the red blood cells. Albumin and granular casts were frequently encountered in the urine during the febrile stage of the disease, but we observed no signs of renal insufficiency. Perhaps the proper hydration and the maintenance of an efficient electrolyte balance may have contributed in preventing this complication among our cases. The drowsiness and delirium reported among

cases of epidemic typhus treated with PABA<sup>14</sup> were not observed in our cases of endemic typhus.

From our observations on 6 of the patients of the control series, it seems that penicillin in doses of 20,000 units given intramuscularly, every 3 hours, fails to alter the course of endemic typhus in the human. Three patients received penicillin before the initiation of therapy with PABA, without improvement. Sulfadiazine in proper doses was administered to 6 of the controls and 3 of the treated prior to the onset of therapy with PABA. The duration of treatment with sulfadiazine averaged 3.5 days, it being discontinued as soon as the diagnosis of endemic typhus was established. We did not observe either toxic or beneficial effects, but the shortness of the duration of therapy with sulfadiazine, the variability in the severity of the symptoms of endemic typhus, and the small number of cases tested do not warrant the formulation of definite conclusions. It appears, from the study of 19 cases of diseases other than endemic typhus (typhoid fever, influenza, pneumonia, malaria) that PABA does not exert a beneficial effect on their clinical course.

**Comment.** The low incidence of endemic typhus among the colored Puerto Ricans is in conformity with observations among the negro population of the South of the United States.<sup>2</sup> The almost identical distribution of the cases, as regards age, in the 2 series studied, makes the evaluation of the results of treatment with PABA more exact, since it is known that the severity of typhus and the mortality rate increase with age. It is evident that endemic typhus is primarily a disease of the young. This cannot be explained on the basis of greater chances of exposure to rodents, because the mode of life of the indigent Puerto Rican makes exposure to rats equal for

all ages, sexes and races. The most probable explanation is a development of immunity with increasing age.

Our observations show that, in the majority of instances, endemic typhus as seen in Puerto Rico is characterized by an abrupt onset with chills, fever, headache, general body aches, and prostration, and that the disease is amenable to therapy with PABA, as evidenced by the difference in the course and duration of the disease in the 33 treated cases as compared with the 27 controls. An analysis of the data tends to indicate that early treatment with PABA should be emphasized.

The fact that 5 of the patients developed the rash during the course of therapy and 7 others after disappearance of the fever, and after convalescence had seemingly started, lends itself to speculation on the mode of action of PABA, and on the pathogenesis and immunology of the disease. The observation seems to indicate that PABA fails to interfere with the pathologic alterations in the vascular system of the diseased, and that once the rickettsiae are fixed in the tissues their destructive action continues for a time in spite of the drug. The rapid favorable response observed in some cases may indicate an attenuation of the toxemia produced by the rickettsiae, the drug being suppressive but not curative. From these results we can suggest that PABA acts as any other antibiotic, inhibiting the growth and multiplication of the organisms, probably in an indirect manner. Perhaps the action of PABA on endemic typhus is comparable to that of penicillin in pneumonia. The latter promptly reduces the toxic manifestations of the disease, while the pathologic process continues its natural, though perhaps abbreviated, course. It is possible, therefore, that PABA attenuates the

activity of the rickettsiae but does not kill the organisms outright, thus allowing the host's natural defensive mechanisms to eradicate the infection through the establishment of an immunity. That the final disposal of the rickettsiae is a function of the host, and that it is aided only in part by the drug, is evidenced by the secondary rises in temperature observed among the great majority of the untreated, and in some of the treated patients. Such rises probably represent minor recrudescences of the disease at a time when immunity is not yet solidly established. It may be noted that such rises are at times accompanied by a recurrence of symptoms of typhus, but these are milder than before. It was noticed that most of the patients presenting this manifestation received the drug late in the course of the disease, which may indicate that the pathologic process was too far advanced for an effective destruction of the rickettsiae by the host aided by the drug. The phenomenon was observed in 2 patients in whom treatment was instituted early in the disease. In these, the clinical response was very effective, and the rash appeared after the termination of treatment, while the secondary rise in temperature occurred on the 7th and 8th days of illness, respectively. The total dosage in these cases was 44 and 98 gm., respectively. Whether larger doses would have prevented the appearance of this secondary rise in temperature, remains a moot question, but we believe that once the rickettsiae have invaded the reticulo-endothelial tissues, and have multiplied enough to produce the clinical manifestations of an already established pathologic process, the fundamental disease process will follow its course, no matter how much PABA is used. This is evidenced by the appearance of the rash even after and

during prolonged treatment with the drug.

The possibility exists that the rickettsiae of endemic typhus are not completely destroyed by the body. It is possible that endemic typhus may behave like epidemic typhus in which a delayed recrudescence, as exemplified by Brill's disease, may occur. Perhaps the rickettsiae of endemic typhus remain in a dormant state and that minor febrile illnesses which pass undiagnosed may be recurrences of the disease. It appears, from the data presented in this paper, that the immunological reaction of the body is very little altered by the administration of PABA, as indicated by the invariable increase in the titer of the Weil-Felix reaction in the treated cases.

The drug is well tolerated, and it represses the manifestations of the disease, but the absence of toxic symptoms in our series of patients does not guarantee the free use of PABA without repeated blood studies to determine the levels of total white cells and observations on the renal function of the patient before and during treatment. This should be done until more knowledge is accumulated on the toxicity of the drug. The conclusion that penicillin is of benefit in experimental typhus<sup>4</sup> has not been confirmed in human endemic typhus. From our limited observations on this point in the control series, it appears that this drug failed to alter the course of the disease. It may be beneficial in preventing bacterial complications, but these are so infrequent in endemic typhus that its use is not warranted until they arise. Sulfadiazine did not seem to alter the clinical picture in our test

cases, but our series is perhaps too small to warrant arriving at a definite conclusion.

**Summary and Conclusion.** Thirty-three patients suffering from murine typhus were given heavy doses of para-aminobenzoic acid for variable intervals and at different stages of the disease, the clinical course being compared with that of 27 untreated cases. An analysis of the data gathered in the course of this study tends to demonstrate that:

(1) Patients with endemic typhus can tolerate large doses of para-aminobenzoic acid for as long as 9 days, and in total amounts as high as 219 gm. without toxic manifestations.

(2) The duration of the disease is considerably shortened by the administration of the drug, especially when therapy is started within the first week of onset of the disease.

(3) The severity of the symptoms of murine typhus is modified within the first 24 to 48 hours after the initiation of treatment.

(4) The drug probably fails to alter the fundamental pathologic process, but aids in the abatement of the toxic manifestations, and, perhaps indirectly, controls the growth and multiplication of the rickettsiae.

(5) The drug does not seem to affect the immunological response of the body to infection with the rickettsiae of murine typhus.

It can be concluded that heavy doses of para-aminobenzoic acid are safe and beneficial in the management of murine typhus, especially when treatment is started early in the course of the disease.

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## KALA-AZAR: 3 CASES DEVELOPING IN VETERANS\*

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PRIOR to World War II few cases of kala-azar were reported in the United States and in each instance it had been contracted in a part of the world where the disease is endemic.<sup>1,3,4,5</sup> During World War 2 many of our military personnel served in endemic areas and among these several cases of kala-azar were observed. A comprehensive review of this disease, along with reports on 30 cases seen among army personnel, has recently been made by Most and Lavietes<sup>2</sup>.

The following cases are presented to call attention to the fact that an occasional isolated instance of this disease may be encountered in the United States among former military personnel. Because the incubation period of kala-azar is not definitely known, one can not state with certainty the length of time that may elapse before symptoms develop following exposure in an endemic area. Thus, unless one is aware of this disease, the diagnosis is likely to be overlooked. This is important from a therapeutic standpoint, inasmuch as therapy is specific, and in most cases a complete cure is effected.

From December, 1945, to March, 1947, 3 cases of kala-azar were seen in this hospital. All 3 represent the typical clinical and laboratory findings that are usually seen, as well as the dramatic response to specific therapy.

**Case Reports—CASE 1. *Present Illness:*** L.P., a 25 year old white male was admitted to the hospital December 6, 1945. He was discharged from the army in August 1945 and felt well until 2 weeks prior to admission when he first noticed increasing fatigue while at work. Within 24 hours he began having chills followed by fever and for this reason he thought he was having a recurrent malarial episode. During the following 2 weeks he became worse, however, and in addition to daily chills and fever he developed swelling of his feet and ankles, shortness of breath on exertion, anorexia, progressive malaise and there was a noticeable increase in the size of his abdomen. There had been no nausea or vomiting but an occasional abdominal pain had occurred.

***Past History:*** He had 10 malarial episodes while in the service, the last attack being in April 1945. No other illnesses were recorded.

He served with the army in North Africa in the Casa Blanca and Oran areas from July 1943 to September 1943, and in Sicily and Southern Italy from September 1943 to January 1944. He was captured by the Germans at Anzio January 30, 1944 and was a prisoner of war in Germany until liberation in April 1945. Thus, early January 1944 was the last possible exposure to kala-azar in an endemic area. Inasmuch as symptoms did not develop until November 1945, the incubation period in this case is assumed to be from 21 to 22 months.

***Physical Examination:*** On admission the patient appeared to be acutely ill, temperature was 103°, pulse 110, and respirations 18. The spleen was tender and palpable to the mid-line and in the left iliac region. There was slight tenderness over a soft liver, and it was palpable 5 cm. below the right costal margin. There was bilateral pitting edema of the lower extremities, particularly about the ankles.

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**Hospital Course:** For the first month of hospitalization the patient remained acutely ill. He had daily fever and his appetite remained poor. The red blood count ranged between 2.01 million and 1.87 million. The white blood cells dropped as low as 1000 with 44% neutrophils and 56% lymphocytes. There was no response to liver or iron therapy. Blood smears for malaria parasites were negative. Blood cultures for *L. Donovan*i were negative. Three weeks after admission the formol-gel test was strongly positive. A sternal puncture was performed and an attempt to demonstrate Leishman-Donovan bodies by smear and culture was unsuccessful. It was believed that despite the inability to demonstrate *L. Donovan*i up to this point, sufficient clinical and laboratory evidence was present to warrant specific therapy, particularly in view of the

spleen was still palpable but much smaller and less tender than at time of discharge. Red blood count was 3.97 million with 81% hemoglobin. The white blood count was 12,600 with a normal differential.

This patient was not seen again until April 1948, some 27 months after completion of treatment. He had enjoyed good health in the interim and had had no reason to seek medical attention. The liver and spleen were not palpable and no abnormal physical findings were noted. The red blood count was 4.27 million with 98% hemoglobin. The white blood count was 9800 with a normal differential count. Total serum proteins were 6.4 gm. (albumin 4.8 and globulin 1.6). He appeared to be in excellent health.

**CASE 2. Present Illness:** D.O., a 22 year old white male was admitted to the

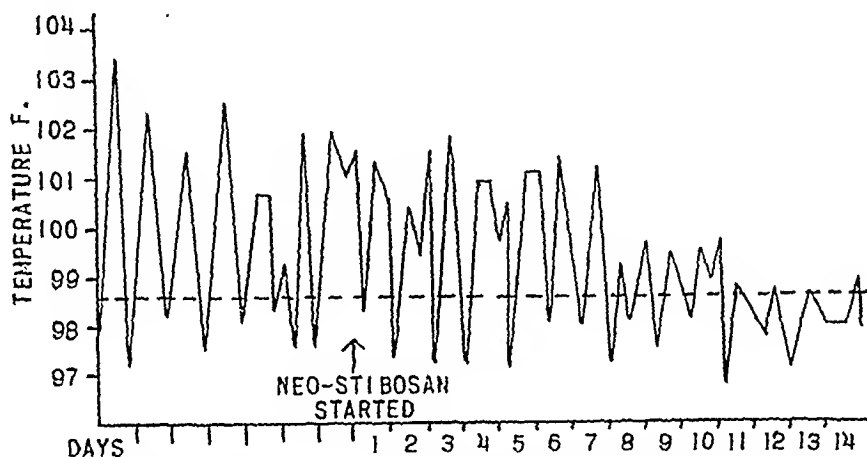


FIG. 1.—Case 1. Temperature chart 1 week before and 2 weeks after beginning specific treatment.

critical condition of the patient. On January 4, 1946 intravenous neostibosan was begun. It was continued in daily administrations until January 22, 1946, at which time a total of 6.0 gm. had been given. Temperature became normal on the 11th day and he remained afebrile (See Figure 1.) After the first week of treatment the patient began to show clinical improvement. The appetite was returning and he appeared less lethargic. On the 12th day of treatment the spleen and liver were smaller and less tender. On the day specific therapy was completed, the red blood count was 4.06 million with 81% hemoglobin. The white blood count was 6350 with a normal differential. He was discharged from the hospital January 30, 1946, 26 days after starting specific therapy with neostibosan.

On examination one month later he felt well and had gained weight and strength. The

hospital February 18, 1946. He felt well until 6 days prior to admission when he developed a shaking chill followed by a high fever, slight headache and backache, and a non-productive cough. The following day there was another shaking chill and the fever persisted. Three days after the onset, nausea and vomiting occurred with some frequency. Because of the similarity to previous malarial episodes, patient took about 1 gm. of atabrine in divided doses prior to admission. This was of no apparent benefit and the elevated temperature continued, although there were no chills after the 2nd day of illness.

**Past History:** There was a history of recurrent malaria while in the military service with the last episode 8 months prior to admission. The patient was in the Marine Corps and spent 8 months in Central Burma, and 14 months in India in the Calcutta, Bombay,

Assam area. He left India about 14 months prior to the onset of the present illness and has not been in an endemic area since.

*Physical Examination:* On admission the patient was flushed and appeared to be acutely ill. The temperature was 100.2°, pulse 100, respirations 20. The spleen was palpable on deep inspiration and was firm and tender. There were no other significant physical findings.

*Hospital Course:* For 3½ months this patient remained a diagnostic problem. Although kala-azar was suggested as a possibility, it was felt that the evidence was not sufficient to warrant specific therapy. The patient became progressively worse, running

tures of the stool and urine for pathogens, repeated blood agglutination studies, examination of the peripheral blood and bone marrow for Leishman-Donovan bodies, blood cultures, spinal fluid examinations and cultures, serum protein determinations and formol-gel tests. In the meantime the patient developed an anemia and a progressive leukopenia which reached a low of 600 WBC. There was a gradual reduction in neutrophils to a low of 14%. Frequent blood transfusions became necessary when other supportive measures failed.

On June 6, 1946, 3½ months after admission, the formol-gel test was positive for the first time. Serum protein studies revealed a



FIG. 2.—Leishman-Donovan bodies in stained smear of the splenic substance, Case 2. (Photomicrograph, X 990).

a high fever with elevations sometimes as high as 104°. Severe shaking chills were frequent. The spleen gradually increased in size until it extended well below the umbilicus and was markedly tender. Liver was tender and palpable 3 cm. below the right costal margin. Anorexia progressed and the patient would take only small amounts of liquid by mouth and even then nausea and vomiting was a frequent occurrence. Marked weight loss was evident and the patient gradually assumed a moribund appearance. During this period the following laboratory procedures were repeatedly investigated in an effort to establish the diagnosis. Frequent blood smears for malarial parasites, smears and cul-

tures of the stool and urine for pathogens, repeated blood agglutination studies, examination of the peripheral blood and bone marrow for Leishman-Donovan bodies, blood cultures, spinal fluid examinations and cultures, serum protein determinations and formol-gel tests. In the meantime the patient developed an anemia and a progressive leukopenia which reached a low of 600 WBC. There was a gradual reduction in neutrophils to a low of 14%. Frequent blood transfusions became necessary when other supportive measures failed.

total of 7.2 gm. (albumin 3.0 gm. and globulin 4.2 gm.). On June 8, a splenic puncture was performed and Leishman-Donovan bodies were found in smears of the aspirated material (See Figure 2). Treatment with neostibosan was instituted immediately. A total of 7 gm. was given in 2 courses. Five gm. were given in 17 days and patient was allowed 1 week of rest. An additional 2 gm. were then given in 7 days. He showed no signs of drug toxicity during or after therapy.

Twelve days after specific treatment was started, the fever disappeared and did not recur during the remaining hospital stay (See Figure 3.) When therapy was completed the spleen had been reduced markedly in size

and was much less tender. His appetite had returned and a weight gain was noted. During the last 2 weeks of hospitalization an average weight gain of 1 pound per day was recorded. The blood picture had become normal (See Figure 4). Five weeks after starting specific treatment the patient was discharged. At that time the liver could no longer be palpated and the spleen edge could be felt 4½ cm. below the left costal margin and it was only slightly tender.

The patient was examined 1 month after discharge at which time further gain in

weight and strength was noted. The blood picture as well as serum proteins were normal. The formol-gel test was negative and serum globulin no longer elevated. The tip of the spleen was palpable only on deep inspiration and was no longer tender. This was the last time it was ever felt.

The patient has been followed for a 2 year period and there is no evidence of any residuals. All laboratory studies have remained normal and the patient looks well and appears to be in excellent health.

CASE 3. *Present Illness:* C.A.B., a 39

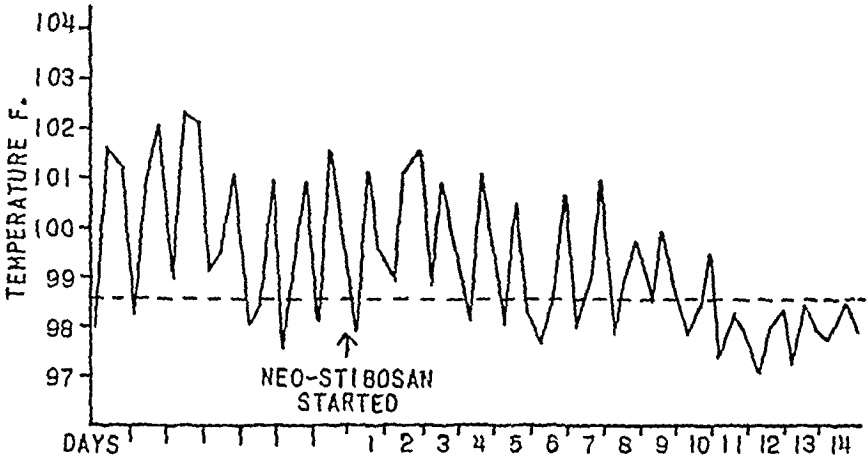


FIG. 3.—Case 2. Temperature chart 1 week before and 2 weeks after beginning specific treatment.

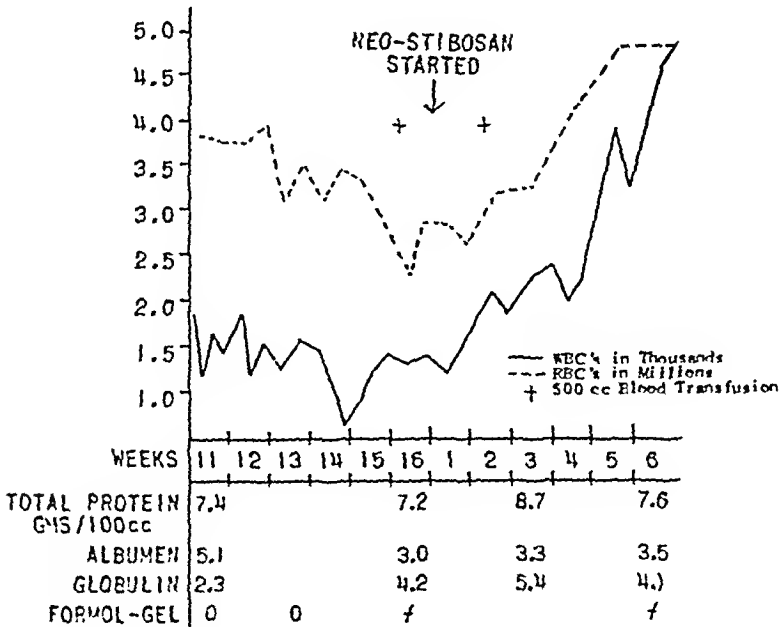


FIG. 4. Case 2. Laboratory data 6 weeks before and 6 weeks after beginning treatment.

year old white male was admitted to this hospital March 4, 1947 complaining of weakness and fever. The onset of his illness was 3 months prior to admission when he developed mild influenza-like symptoms which persisted for about a week. He felt well for 1 week after which he became acutely ill with chills and fever as high as 106°. He was hospitalized in another institution for 1 month where sternal puncture was included in the studies but a diagnosis was not established. During this period he became progressively weaker and "felt near death". The chills and fever persisted. Six blood transfusions were given with some improvement including decrease in height of fever. After discharge from that hospital he continued to improve at home

ately pale, emaciated, appeared chronically ill and spoke in short interrupted phrases, apparently due to weakness. The skin was slightly yellow (he had been taking atabrine for about 6 weeks), there were petechiae on the feet and ankles, and a marmoraceous erythema on the hands. There was generalized non-tender lymphadenopathy. The lower borders of the spleen and liver could be visibly outlined through the thin abdominal wall, each being 7 cm. below the rib margin on inspiration; each was firm and non-tender. There was a small retinal hemorrhage near the left macula and there were bloody crusts on the left side of the nasal septum. The remainder of the examination was essentially negative.

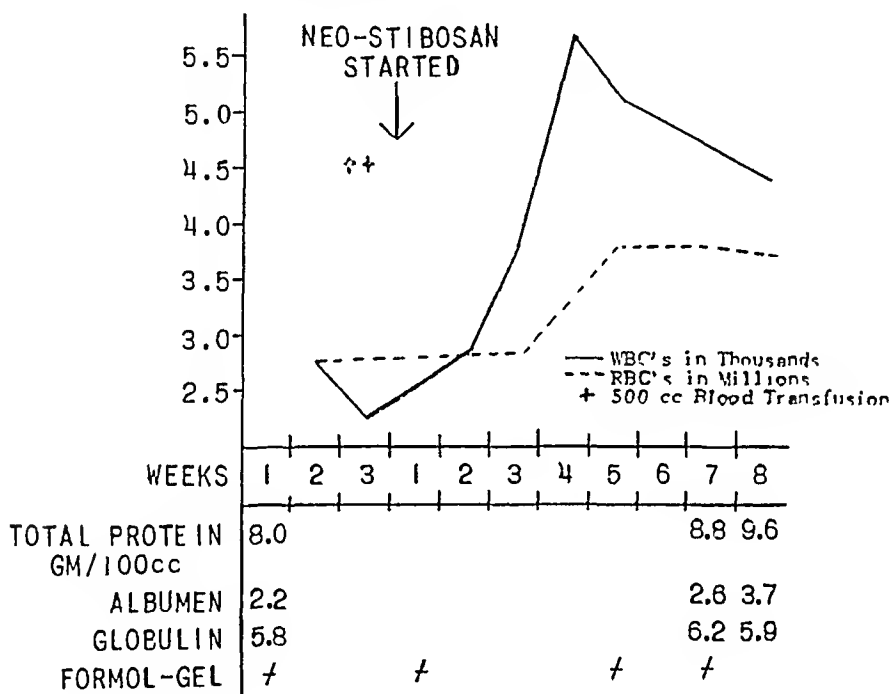


FIG. 5.—Case 3. Laboratory data, entire hospitalization.

for 2 weeks but his severe symptoms returned and he was hospitalized at a second hospital on February 23, 1947, where the diagnosis of kala-azar was suspected. The patient refused sternal puncture at this time. He was given 6 more blood transfusions and transferred to this hospital. During the preceding few weeks he had complained of recurrent epistaxis on slight trauma.

*Past History:* While in the army he served 20 months near Calcutta, India, leaving in early July 1945, 17 months prior to the onset of symptoms. He had not been in an endemic area since that time.

*Physical Examination:* On admission temperature was 101.8° orally, pulse 110, respiration 28, B.P. 110/70. He was moder-

*Hospital Course:* Anemia was essentially normochromic (See Figure 5). Leukopenia was largely at the expense of the neutrophils which were 40 to 50%, while lymphocytes were 50 to 60%. Bleeding and clotting time were within normal limits but there was no clot retraction after 48 hours. The platelet count ranged from 44,000 to 82,000 during the hospital course except for 1 count of 178,000 during the 4th week of treatment. Kahn test, malaria smear, and routine blood culture were negative. Heterophile agglutination, RBC fragility, prothrombin time and urinalyses were within normal limits. Chest X-ray revealed questionable enlargement of the left mediastinal lymph nodes. ECG showed left axis deviation but was otherwise

normal. Repeated blood smears and 2 sternal marrow smears were negative for Leishman-Donovan bodies. Cultures of the blood and sternal marrow on NNN media were negative for flagellates.

Splenic puncture performed on March 17, 1948, was preceded and followed by a 500 cc. blood transfusion. Leishman-Donovan bodies were found in the smear of the splenic substance.

The patient had daily afternoon fever but the morning temperature was always normal. Treatment with neostibosan was begun on the 21st hospital day and was given I.V. daily for a 26 day period, a total of 6.9 gm. being administered. Temperature became normal on the 11th day of treatment and he was afebrile after that time (See Figure 6). His weight on the 15th hospital day was 115 pounds;

the first two visits, 5 and 6 months after treatment, the liver was 3 cm. below the rib margin and the tip of the spleen was easily palpable on deep inspiration. Complete blood count and clot retraction were normal. Platelet count was 150,000. Formol-gel test was negative. Serum proteins were 8.1 and 8.8 gm./100 cc. with an A/G ratio of 1/1. Thymol turbidity was elevated and cephalin flocculation was 4+. On the third visit, 8 months after treatment, the liver was not palpable and the tip of the spleen was barely palpable on deep inspiration. Serum proteins were 7.7 gm./100 cc. with an A/G ratio of 1.9/1. Cephalin flocculation was 3+ but the other liver function studies were normal. When last examined, 13 months after treatment, the spleen and liver were not palpable and all laboratory tests were within normal limits.

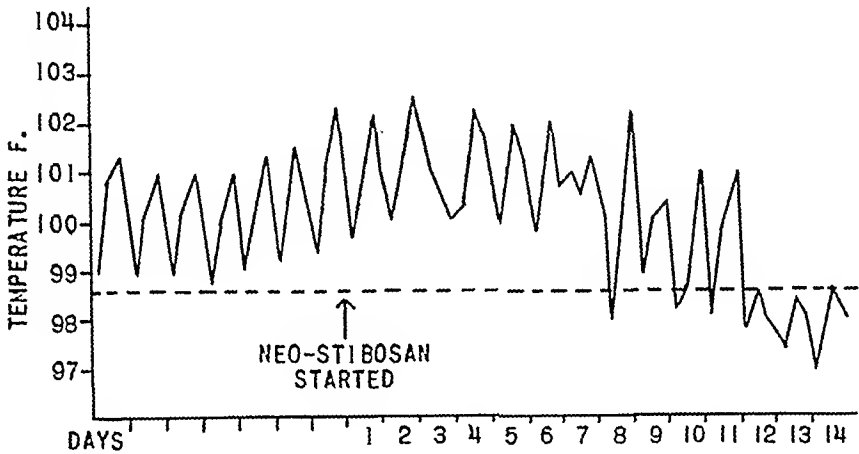


FIG. 6.—Case 3. Temperature chart 1 week before and 2 weeks after beginning specific treatment.

after therapy for 2 weeks he weighed 126 pounds. During the 3rd week of therapy he was up and about much of the time. The petechiae gradually disappeared as did the retinal hemorrhage and the epistaxis. The spleen began to decrease in size during the 3rd week of treatment and the liver became smaller during the 6th week. He developed a moderate alopecia of the scalp during the 5th week but hair subsequently returned. At the time of discharge, 8 weeks after therapy was started, his weight was 134 pounds and he complained of only slight weakness. On expiration the lower border of the spleen was felt at the rib margin and the liver was 5 cm. below the right costal margin. There was no lymphadenopathy.

This patient returned to work as a truck driver a few weeks after discharge and has since been examined on four occasions. On

**Discussion.** The diagnosis of kala-azar, even though suspected, may at times be difficult to prove. This is illustrated in Case 1 where Leishman-Donovan bodies were never found. The response of this patient to specific therapy, however, justifies the diagnosis. In the other two patients a splenic puncture had to be done before the diagnosis could be established. This procedure, done properly, carries little risk, and indeed at times may be instrumental in saving the patient a far more serious operation. A case in point in which a splenectomy was performed has been reported<sup>6</sup>. In this in-

stancce pathological examination of the spleen established the diagnosis of kala-azar. If the laboratory data are suggestive and there is a history of having been in an endemic area, it is felt that the relatively safe procedure of splenic puncture is justified, even if other examinations have failed to demonstrate Leishman-Donovan bodies.

The drug of choice in the treatment of kala-azar is neostibosan, according to Most and Lavietes<sup>2</sup>, and the results obtained in our 3 cases lend added weight to this statement. Neostibosan is a pentavalent antimony compound supplied in powder form in single dose ampules. At the time of administration it is dissolved in either sterile saline or distilled water to make a 5% solution, and is given intravenously. The drug was 100% effective in producing a cure in our 3 cases and no relapses have occurred.

**Summary.** 1. Three cases of kala-azar were seen in this hospital from December, 1945, to March, 1947, and are reported in detail.

2. The minimum incubation period in these cases ranged from 14 to 21 months.

3. Attention is called to the possibility of encountering isolated instances of this disease and the likelihood of overlooking the diagnosis because of its infrequency in the United States.

4. In patients in whom the disease is suspected but confirmatory evidence is lacking, splenic puncture is recommended as a relatively safe procedure. Leishman-Donovan bodies can be found in most cases by direct smear or culture of the splenic material.

5. Treatment with neostibosan is specific and almost 100% effective in producing a complete cure.

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# STREPTOMYCIN IN THE TREATMENT OF TUBERCULOUS ENTERITIS, A REPORT OF THIRTY-THREE CASES

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ALTHOUGH it is scarcely more than 3 years since the discovery of streptomycin was announced from Waksman's Laboratory in 1944<sup>1</sup>, a very considerable understanding has already been gained concerning its limitations and usefulness. The progress has been much more rapid than was the case with penicillin: partly because the manufacturing houses profited by the very painful experiences encountered in the production of that drug; partly because of the several large scale co-operative investigations into its effectiveness which were launched after the pioneering work of Hinshav and his collaborators,<sup>2,3</sup> which disclosed its promise in the treatment of tuberculosis. One of these investigations has been conducted within the structure of the Veterans Administration. It was launched in June of 1946 in co-operation with the Army and Navy and was at first directed toward the effects of streptomycin upon pulmonary tuberculosis. Soon it was extended into other forms of the disease and the preliminary findings of 22 participating hospitals were recently<sup>4</sup> recounted in a report to the Council on Pharmacy and Chemistry of the American Medical Association.

Very considerable masses of clinical

material were available to the investigators in the commoner forms of tuberculosis and it was not difficult to reach, at least tentatively, conclusion as to the effectiveness of streptomycin under these circumstances. In the case of less common lesions, the situation was difficult, since no single hospital had more than a few cases under treatment. This was the situation in the instance of tuberculous enteritis for, although it was formerly a common complication of active pulmonary tuberculosis, there were only a few cases under treatment in any one hospital. It was therefore resolved by the Veterans Administration's Third Streptomycin Conference in May of 1947 that the experience of all hospitals be collected and the results of this experience be published in a single paper. The present authors were invited to undertake this task since, at the time the decision was made, the hospital with which they are connected had treated more cases of tuberculous enteritis than any other Study Unit. No co-operation of this sort can be as satisfactory as if all the cases had been treated under the authors' supervision, but it is believed that the large volume of information gathered is sufficiently complete to permit certain conclusions. We wish to

record our admiration and gratitude for the readiness with which this material was furnished to us.\*

**Selection of Cases:** All tuberculosis cases which have come under the care of the Veterans Administration Streptomycin Research Program have been treated according to the provisions of protocols which were prepared by the Central Office Streptomycin Committee with the concurrence of the investigators. With very few exceptions, these protocols have required bacteriologic or pathological proof of tuberculous etiology. Tuberculous enteritis is, by necessity, one of these exceptions. The impossibility of providing an absolute diagnosis constitutes the weakness of this presentation. The protocol governing treatment of tuberculous enteritis permitted the use of streptomycin in patients with proven pulmonary or extrapulmonary tuberculosis who had characteristic gastro-intestinal symptomatology together with radiologic evidence of an intestinal lesion which could be reasonably considered tuberculous. The difficulty of establishing an absolute diagnosis of this complication is not peculiar to our experience but is well recognized. There are other ulcerative intestinal lesions and, an added complication, several of these respond favorably to treatment with streptomycin<sup>1,5</sup>. More important, there is also the possibility that in any such series as this the symptomatic relief which is observed could be attributed to a diminution of toxicity resulting from the effects of streptomycin upon the pulmonary disease. However, the presumptive nature of the diagnosis being acknowledged, the existence of severe intestinal symptoms in patients with proven pulmonary tuberculosis, together with radiologic evidence, establishes strong *prima facie* evidence for the accuracy of the diagnosis in the group as a whole.

**Clinical Material:** Although the 33 male patients ranged in age from 20 to 58, 20 of them were living in their third decade.

Twenty-nine were white, 3 were negro and 1 was Mexican. The mean known duration of the coexisting pulmonary disease was 19 months. All had far advanced pulmonary tuberculosis with the exception of Cases 8, 24, 29, and 32, who had moderately advanced pulmonary tuberculosis. Cavities were described in 21 cases and in only 3 cases was there a definite statement that cavities did not exist. Positive cultures of sputum or gastric washings were reported from all 33 patients at some time during the course of their intestinal disease and except in Case 8 (See case reports) the pulmonary disease was considered active at the time streptomycin was instituted.

Intestinal symptoms had been present from 4 to 6 months prior to streptomycin therapy in 12 of the patients, the mean duration being 5 months for the entire group. The textbook picture is more usually seen in this disease than in most diseases. With a few exceptions, covered in the case presentations below, all cases had the usual symptoms of either diarrhea or constipation or alternating constipation and diarrhea, abdominal pain, abdominal soreness, loss of appetite, weakness, nausea and occasionally vomiting together with the physical findings so familiar to the phthisiologist since the time of Hippocrates. In 4 of the patients tuberculous appendices had been removed, thus adding to the probability of an accurate diagnosis. Although no detailed analysis was made of extrapulmonary disease, tuberculosis laryngitis was reported in 2 instances, and, in an additional 2 patients rectal fistulae were present.

**Regimen:** The daily dose employed in this series has not been uniform but has varied between 1.0 and 2.0 gm. Within this range no difference in response has been observed when the intramuscular route was used. At the present time 1 gm. is recommended in 2 doses. The lower dosage carries only a 23% inci-

\* VAH, Barnes Annex, Vancouver, Wash., 1 case; VAH, Brecksville, Ohio, 1 case; VAH, Butler, Pa., 1 case; VAH, Castle Point, N.Y., 4 cases; VAH, Dayton, Ohio, 1 case; VAH, Hines, Ill., 1 case; VAH, Livermore Cal., 1 case; VAH, Memphis, Tenn., 1 case; VAH, Minneapolis, Minn., 4 cases; VAH, Nashville, Tenn., 1 case; Northern Permanente Hospital, Vancouver, Wash., 3 cases; VAH, Richmond, Va., 5 cases; VAH, Rutland Heights, Mass., 4 cases; VAH, Van Nuys, Cal., 1 case; VAH, Wadsworth, Kan., 4 cases.

dence of vertigo as compared with a 94% incidence when 2 gm. daily are used.<sup>1</sup>

Oral treatment, 2 gm. per day in 5 doses, was used in treating 2 patients for 66 and 120 days. Four and six weeks elapsed before complete relief of symptoms was obtained as compared to one week when intramuscular treatment was used. The advantage of the oral route would lie in the non-absorbable property of the drug and the consequent possibility of avoiding toxic manifestations and the development of resistant organisms. These 2 patients, however, both showed significant blood levels, suggesting that the diseased gut may have acted differently than normal bowel in this respect. Further study of the oral route, blood levels, and development of resistant organisms in the stools and in the sputum of these orally treated cases is indicated. The additional patients receiving the intramuscular course of therapy had been previously tried on 2 gm. oral doses for 14 days without adequate response. Perhaps 14 days is an inadequate trial period for oral therapy. A 5th patient (Case No. 21) received oral treatment and showed improvement during the 1st week but was subsequently shifted to intramuscular therapy when signs of bowel obstruction developed.

There was also little uniformity in the length of treatment of these cases. Nineteen patients completed courses of 60 to 120 days. Fourteen-day courses were used in 6 cases with the design of merely providing symptomatic relief. Eight cases are still under treatment, having received 31 to 86 days of streptomycin.

**Clinical Results.** Streptomycin has been uniformly effective in the relief of symptoms of tuberculous enteritis in this series, although several of the participants in this study were highly skeptical when their first cases were started on the drug. A few cases were actually being treated primarily for other than intestinal disease when the relief of severe coexistent intestinal symptoms called attention to its effectiveness in this disease. If one considers the ineffectiveness of streptomycin in

chronic, far advanced, avascular, caseating and fibrotic pulmonary lesions, it is not surprising that skepticism existed toward the effect of streptomycin in similar cases complicated by a secondary ulcerating tuberculous ileocolitis. A glance at the accelerating downward course of pre-streptomycin weight curves in these patients indicates the expected outcome. The morose attitude engendered by experience as old as the disease itself is succinctly epitomized by the Hippocratic teaching that, "Diarrhea attacking a person with phthisis is a mortal symptom."

After the initiation of treatment by the intramuscular route, improvement was noticed almost immediately. In 20 cases 1 week was quoted by the investigator as the period during which maximum benefit was reached. Four investigators mentioned 3 days as the period when abdominal pain was completely relieved. In the remaining cases the relief of abdominal symptoms was summarized as, "Relief of abdominal pain and distention in 4 days, no distress after 31 days"; "Relief immediate"; "Relief only slight on oral therapy, complete on intramuscular"; and these comments are repeated in reports by various investigators. Increases in appetite were frequently described as very marked and tremendous after the 1st week of treatment.

The effect on symptoms is best illustrated by quoting in greater detail the pertinent information from several typical cases:

**Case Reports.** Case 3, E.A., 20-year old Mexican male, got 1.8 gm. per day in 4 doses for 60 days. Chronic abdominal distress, nausea and vomiting and extreme weakness disappeared within 24 hours. Within 4 days he began to eat much better and within 7 days his appetite was tremendous, not only for meals but for small feedings between meals. Within 7 days the stools had diminished in number from 4 or 5 liquid stools a day to 3 soft stools. On the 12th day there

were no stools. Thereafter the stools were normal in number and consistency.

Case 4, D.K., 22-year old white male, received 1.8 gm. a day in 6 doses for 120 days. Five days after specific medication began, the abdominal cramps subsided and appetite began to improve. In 2 weeks the diarrhea (3 to 5 mushy brown stools daily) and belching disappeared, the stools became formed and the patient had 1 bowel movement a day. This improvement, accompanied by a decrease in sputum from 8 ounces to 1 ounce a day, continued for the 4 months of treatment and 4 months of follow up after streptomycin was stopped.

Case 5, A.G., 25-year old white male, was given 1 gm. a day in 5 doses for 120 days. Improvement was noticed by the patient practically from the time streptomycin was started and the only complaints after the first few days were occasional mild cramps reported on the 46th and 48th day of treatment. These cramps caused considerable fear and worry on the part of the patient, but the

continued freedom of symptoms thereafter soon restored his cheerfulness.

Apparently the skepticism of the physician is communicated to or shared by some of these patients and the mildest return of symptoms causes great anxiety. This was also seen in Case 2 which will be presented with the more detailed case reports below.

Relief of diffuse and localized abdominal tenderness, rigidity, and distention came within a few days after relief of symptoms. One case had relief of pain and right lower quadrant tenderness and disappearance of a right lower quadrant mass within the first 2 weeks of treatment. In 18 patients, an episode of diarrhea was present at the time streptomycin was started. In these cases the liquid stools became progressively soft and then formed and were reduced in number from an average 6 per day to an average of 2 per day by the end of the 1st

## TUBERCULOUS ENTERITIS

## TEMPERATURE CHART

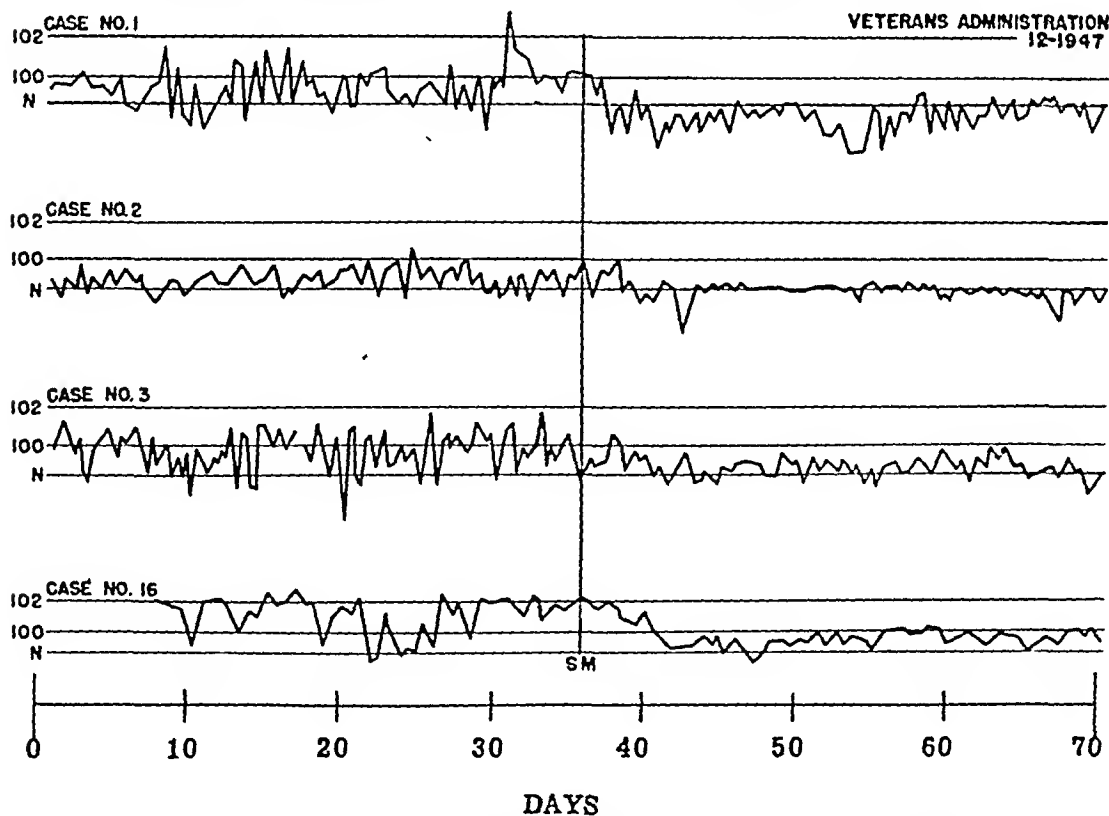


Fig. 1.—Effect of streptomycin therapy on fever in tuberculous enteritis.

SM = Streptomycin therapy begun.

week. One case having 12 liquid stools before treatment had only 2 soft stools within the first 3 days of treatment. Where stool odor was mentioned as being unbearably offensive there was a return to a normal fecal odor. The presence of occult or gross blood, mucus, and pus was mentioned in only 8 cases and disappeared as the stools became normal.

anticipated in patients who had lost no weight recently. Conversely, in those patients who had recently lost rapidly from their disease a rapid gain in weight could be expected, the cases being provided specific treatment. Figure 2 demonstrates the validity of this premise in that rate of gain is shown to be directly proportional to the preceding rate of loss. Taking as a group 21 of

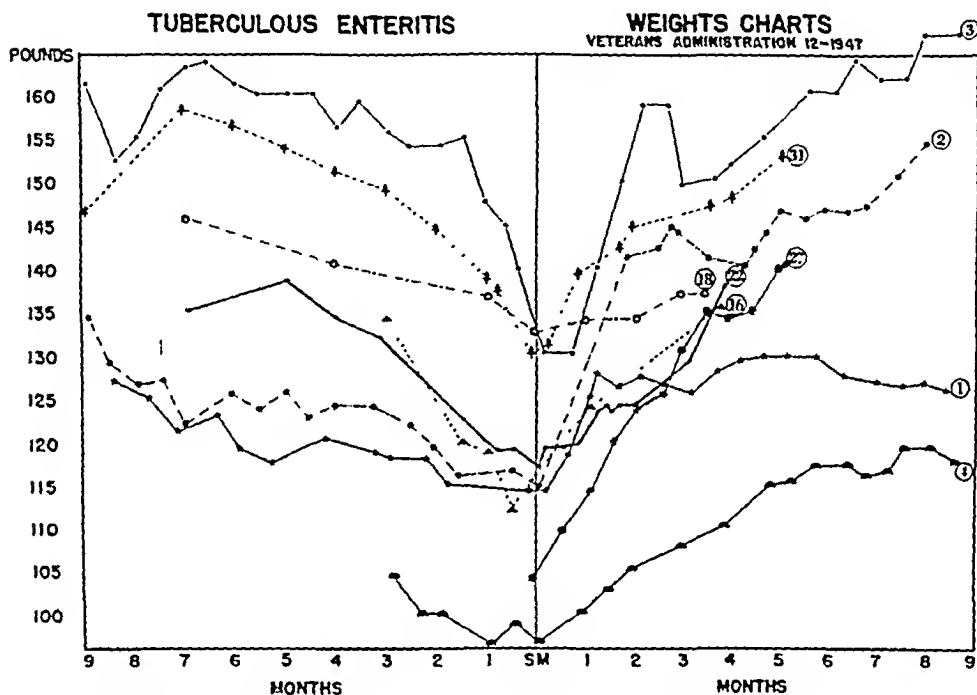


Fig. 2.—Effect of streptomycin therapy on body weight in tuberculous enteritis. SM = Streptomycin therapy begun.

Figure 1 shows the effect of streptomycin treatment on elevated temperatures and requires no further comment except for calling attention to the decrease in diurnal variation which accompanies the return to normal levels.

Weight gain was an especially suitable index of the progress of the intestinal disease, since it directly reflects the ability to ingest, digest, assimilate and retain food as body substance. This is true, of course, only when the intestinal disease is the main cause of asthenia. Little weight gain could be

the 23 cases where adequate weight measurements were reported, it was found that they gained 400 pounds in 88 patient months following the start of streptomycin, or an average gain of 4.7 pounds per month. One patient showed a 15-pound weight gain previous to streptomycin therapy, over a period of 4 months and a loss of 5 pounds during the 1st month of treatment. The 23rd patient failed to gain any weight. In 10 cases weights were not reported or the patients were not weighed because of their weakness and debility or because, being terminal or near ter-

minal, their weight was not considered of importance to those who were treating them.

It is important to analyze the incidence of sputum conversion in connection with the possibility of recurrence. Only 8 of the 33 cases were converted to negative sputum during or after the relief of intestinal symptoms and more intensive study with longer follow-ups will inevitably tend to reduce this number. Conversely, following general improvement from removing the liability of intestinal disease, an undetermined number of otherwise hopeless cases may be able to reach sputum conversion.

Three patients had thoracoplasties for unilateral cavitating tuberculosis after recovering from their intestinal disease. In no case, however, was any collapse therapy introduced during the first 60 days following relief of intestinal symptoms. Case 8 was the only patient who had been able to heal his pulmonary disease previous to the treatment of his intestinal disease. Case 2 was the only patient with a predominantly exudative pulmonary disease of the type which responds best to streptomycin. Although no case had progression of his pulmonary disease during streptomycin treatment, it was obvious that the pulmonary disease was not greatly improved in a majority of cases. This is as expected, since, as already mentioned, the enteritis was usually secondary to rather severe, long standing pulmonary disease of a fibrotic, caseating character, rather than the predominantly inflammatory disease which is expected to respond best to specific chemotherapy.

In 6 patients, streptomycin was used only for relief of symptoms in the presence of obviously hopeless pulmonary disease. In these cases only 14 days therapy was used.

There were 2 cases where a definite

recurrence of symptoms, return of diarrhea or reappearance of blood and mucus in the stools occurred. These cases (No. 2 and No. 9) are detailed below with the other case presentations. A longer follow-up and larger series of cases will be necessary before the rate of remission or recurrence can be well established. Eight patients are still under treatment and 25 have been followed, 1 to 16 months since their treatment was started or 2 weeks to 12 months from the time streptomycin was discontinued. Of the patients whose treatment had been completed the average follow-up was 6½ months. One of the terminal patients, who was treated only for relief of symptoms, died. However, during the 14 days of follow-up there was relief of abdominal pain, and the twelve liquid, foul smelling, incontinent stools a day were reduced to 2, thus eliminating much of the nursing problem, including prevention of bed sores. Without doubt the patient's last days were made more tolerable.

A few of the more informative cases have been chosen for a more detailed account. The reason for their selection will be given in each instance. Thus, the first case presented is also the first case treated in this study. It is an example of the disease at its worst, the debility being out of all proportion to the severity of the primary pulmonary disease. With the added assistance of a thoracoplasty for control of his pulmonary disease, streptomycin has permitted this patient to overcome his disease, leave the hospital against medical advice, and carry on a restricted amount of work without, so far, showing any reactivation of either the intestinal or pulmonary disease.

Case 1. K.E., a 21-year old white male with unilateral, far advanced, cavitating pulmonary tuberculosis and pneumothorax failure because of adhesions, had suffered for 8 months with progressively increasing

done in the next day or two, he will have a further course of 14 days treatment with streptomycin for symptomatic relief. This patient still has occasional bouts of streaking. His general condition is poor, but he is not feeble."

The following case, without previous symptoms of intestinal disease, was found at operation for appendicitis to have ileo-cecal and appendiceal tuberculosis. It is interesting to compare this case (No. 20) with case No. 8 above and case No. 32 presented below. All 3 had a tuberculous appendix removed.

Case 20. A 33-year old white male with extensive pulmonary tuberculosis, rather suddenly and without previous abdominal symptoms, developed severe cramping and aching lower quadrant pains. This continued for 24 hours with right lower quadrant tenderness and slight muscle spasm. There was full awareness of the possibility of intestinal tuberculosis, but in view of the immediate history and physical findings, an appendectomy was performed. The appendix, 5 cm. in length and 2 cm. at the base, was filled with thick mucopurulent material. Microscopically there was seen a lumen containing purulent exudate, a markedly expanded submucosa with discrete and conglomerate foci of epithelial cell infiltration, caseous necrosis, giant-cell reaction, scattered tubercles in the muscular coats, and acid-fast bacilli in Ziehl-Neelson stains of the specimens. Streptomycin was started immediately post operatively, at a dosage of 2 gm. in 5 doses a day, and the surgeon waited for the appearance of the expected fecal fistula. No fistula developed. The drain was removed after 7 days. Healing was normal and repeated abdominal examinations revealed no sign of remaining disease. Streptomycin was discontinued after 31 days.

Obviously some cases of this sort can be and have been operated on without complications, even though streptomycin was not used immediately post-operatively. Case No. 24 is of interest in that an appendectomy was success-

fully performed and 60 days elapsed before streptomycin was used. Usually a surgeon should be able to tell from the appearance of the tissues whether a fecal fistula is to be expected.

Case 24. A 20-year old colored male with far advanced, active, pulmonary tuberculosis had a tuberculous appendix removed 60 days before streptomycin was started. Abdominal pain and tenderness was not relieved. There had been no elevation of temperature except during the attack of appendicitis. A gastro-intestinal series, performed 30 days before streptomycin was started showed spasticity and irregularity of contour of the cecum and terminal ileum. Thirty-four days after institution of streptomycin, a gastro-intestinal series showed a decrease in the irregularity and spasticity, and 75 days after streptomycin was started further improvement was seen by Roentgen ray. On this last examination no deformity was visible in the cecum and only a minimal amount of irregularity was seen in the mucosal pattern of the terminal ileum. Abdominal symptoms were mild in this case, but were relieved following the introduction of streptomycin therapy.

Another surgical case, admittedly hard to evaluate, is presented to illustrate the complications which can develop in these patients without streptomycin, and also the possible effect of streptomycin when these complications have had ample time to become established.

Case 32. F.H., a 52-year old white male without symptoms of pulmonary disease, had been admitted for appendectomy 4½ years ago. Following appendectomy a fecal fistula developed. Eight months later, a tuberculous terminal ileum and cecum were removed and a double barreled ileo colostomy was left on the right side. Two years ago the patient was transferred to his present hospital. The distal loop of colon had undergone progressive contraction and had disappeared from the surface of the abdominal wall, leaving the proximal ileostomy draining fecal material. Surgery was again resorted to, and a formal

closure of the distal colon was made. The ileum was involved in more tuberculous inflammatory tissue and was resected. An ileo-transverse colostomy was performed. Following this there were occasional bouts of abdominal discomfort and alternating constipation and diarrhea. Ten months ago the patient was transferred to the Tuberculosis Service because of the appearance of an acinonodose infiltration in the lungs and elevated temperatures.

It should be mentioned for completeness that in addition to the enteritis, otosclerosis had caused severe deafness, more marked during the last 3 years. Tuberculous epididymitis and tuberculosis of the bladder were also present. The urine was often packed with white blood cells. No tuberculous-appearing calyces were seen on retrograde pyelography, but a moderately severe bilateral hydronephrosis was found.

In spite of dozens of examinations, tubercle bacilli could not be found in sputum, gastric washings, urine or feces until 3 months ago when acid-fast bacilli were obtained from a guinea pig inoculated with the patient's urine. Soon thereafter a gastric washing culture grew acid-fast bacilli.

As a further diagnostic and therapeutic procedure (removal or drainage of pus before specific chemotherapy) the patient was persuaded to have his right epididymis removed and tuberculous granulation tissue was found.

During the last 3 months before streptomycin therapy, there developed increasingly severe attacks of intermittent colicky pain associated with borborygmus and the appearance of distended loops of bowel beneath the thin abdominal wall. These attacks came approximately three days apart and lasted for a few hours at first. Finally, they would continue for 10 or 12 hours at a time. They usually ended suddenly and with the passage of watery, extremely foul smelling stools. Often demerol or morphine by hypo was necessary during the attacks. Bismuth and paregoric were ineffective. There was loss of weight, fever, weakness and anemia. Blood transfusions afforded temporary relief from the weakness and anemia.

Courses of penicillin and various sulfa drugs were tried several times without effect. Eighty-seven days ago (written 12-20-47) a course of intramuscular penicillin was started using 50,000 units 3rd hour. Seventy-five days ago streptomycin 0.25 gm., 6th hour, was started. Fifteen days later the streptomycin was changed to 0.5 gm., 12th hour. Twelve days after streptomycin was started the patient reported, for the first time, that in spite of skepticism engendered by 4½ years of continued hospitalization for surgical and medical treatment, he was actually noticing improvement. He had slept for an entire night without abdominal discomfort. His appetite was much improved and he no longer felt obliged to "watch his diet." Examination revealed a much softer abdomen but there was still slight tenderness on deep palpation in the right lower quadrant. Since that time, attacks of borborygmus with pain and visible bowel loop distention have been much less frequent, less severe and of shorter duration, 10 days to 2 weeks of complete comfort passing between attacks. Stools, previously a foul smelling, thin, irritating, dark liquid, have become a normal fecal-smelling, light brown with the consistency of well cooked oatmeal mush. The temperature previously above 99, with almost weekly spikes above 100, became subnormal and has remained around 98 since the first dose of streptomycin. The weight has remained near the low of 116 pounds in spite of improved appetite. The ultimate prognosis remains guarded because of genito-urinary disease. However, the patient has changed from a bitter complaining invalid who was doubled up in pain nearly one-third of the time to a smiling man who slaps his "belly" and reports he "feels better than he has felt in years."

**Influence of Streptomycin On Radiologic Findings.** In 17 cases, the authors examined the roentgenograms and were able to discuss the findings with one of the radiologists at their hospital. A tabulation of findings was attempted but was abandoned as impractical because of the variation in technique



used in various hospitals, the variation of findings seen in the films, and in addition, a generally accepted feeling that fluoroscopic findings were of equal importance with the study of films. Since the impression of fluoroscopic findings is usually included in the Roentgen-ray report these reports have been summarized in 17 cases where sufficient pre- and post-treatment reports have been available. All of these cases showed abnormalities before treatment. In 6 of this group the findings returned to normal after treatment. In 8 cases definite improvement was seen but some residual deformity remained. Two cases (No. 4 and 8) showed marked residual abnormality and 1 case (No. 21) developed signs of small bowel obstruction. Case 4, who had symptoms for 22 months before treatment, showed no demonstrable change by Roentgen-ray in spite of a clinical response which was of the usual promptness and completeness.

The most marked disease radiologically before treatment of any of the cases studied was seen in Case 8 (see clinical summary above), a 28 year old white male who had symptoms for 32 months before treatment. With treatment it would appear that ulceration healed but that contraction of scar tissue caused continued shortening and narrowing in the region of the greatest disease. One patient (Case 21) developed Roentgen-ray signs of small bowel obstruction as has been mentioned above in connection with the discussion of clinical results.

From the radiologic standpoint, there was too much variation in the duration of intestinal disease, duration of treatment and duration of follow-up to draw any conclusion as to the ideal length of treatment. The average time required for maximum radiologic improvement, the effect of duration of disease before treatment on the reversibility of radiologic abnormalities, the

long-term effects of contracting scar tissue on bowel outline, are other, at present, unanswerable questions introduced by this therapeutic innovation. Suffice it to say that radiologic normalcy can be expected provided the abnormalities are primarily those of local irritation, (*i.e.* spasm, hypermotility, loss of haustrations, mucosal irregularity, and others). Where ulceration has been deeper, more wide spread and of longer duration, and where lymphatic obstruction and interstitial inflammation have destroyed normal architecture of the bowel wall, irreversible changes may not only persist, but may cause further distortion due to the contraction of residual cicatrix. This residuum will be of only academic interest unless the continued contraction of scar tissue is shown to lead frequently or even occasionally to bowel obstruction.

Below are presented the summarized Roentgen-ray reports on 17 cases chosen because of adequate pre- and post-treatment examinations with the original interpretations being available. In other respects they are unselected and representative of the entire group including the 17 cases whose films were reviewed by the authors.

Case 1. During 120 days, received intramuscularly 1 gm. per day, after 10 months of symptoms. At 45 days before streptomycin, gastro-intestinal series showed irregular terminal ileum and complete emptying of the entire bowel in 24 hours. At 28 days before streptomycin, barium enema showed narrowing of lumen of entire colon and replacement of normal haustrations by numerous small irregularities of bowel outline, especially in the transverse colon. The cecum was small and narrow, the ileocecal valves irregular and thickened. At 142 days after streptomycin, a gastro-intestinal series showed normal motility and outline. Two days later, a barium enema showed no irritability, obstruction or spasm, and the procedure caused no pain.

Case 2. He received 92 days' intramuscular treatment of 1 gm. per day after 2 months of symptoms. At 17 days before streptomycin, a gastro-intestinal series showed ileal segmentation at 6 hours; at 7 hours the entire meal was in the distal colon. The terminal ileum and cecum were not visualized (Stierlin's sign). At 10 days before streptomycin the barium enema showed easy filling of the distal colon, but poor filling of the right colon, cecum and terminal ileum,

ized and the cecum slightly irregular in mucosal pattern. There was much less irregularity, spasm and irritability. Six days later, the barium enema showed the ascending colon and cecum only partially filled because of the discomfort, and there was persistent slight cecal irregularity, but no spasm or irritability. At 120 days after streptomycin the series showed a well filled terminal ileum, cecum and ascending colon and no irregularity seen. The barium enema still showed slight



Fig. 3.—Case 2. Barium enema 10 days before streptomycin shows a marked disturbance of mucosal pattern in the ileo-cecal area with polypoid changes and granularity.

with rapid rejection of barium by the diseased portion of the bowel. There was a small amount of barium in the terminal ileum. Films showed marked disturbance of the mucosal pattern of the cecal area with polypoid changes extending well up into the hepatic flexure. The remainder of the colon showed granular mucosa (Fig. 3). At 36 days after streptomycin, the series showed abnormal small bowel segmentation, straightening of an ileal segment, terminal ileum not visual-

irritability in cecum and ascending colon, which filled easily as did the terminal ileum, and slight irregularity in cecum and ascending colon, but continued improvement each time. At 180 days the enema study showed only loss of haustrations in the ascending colon and loss of pliability in cecum remaining. A retro-cecal appendix was visualized. Evacuation film showed slight distortion of normal mucosal pattern in the ascending colon. At 300 days after streptomycin, a

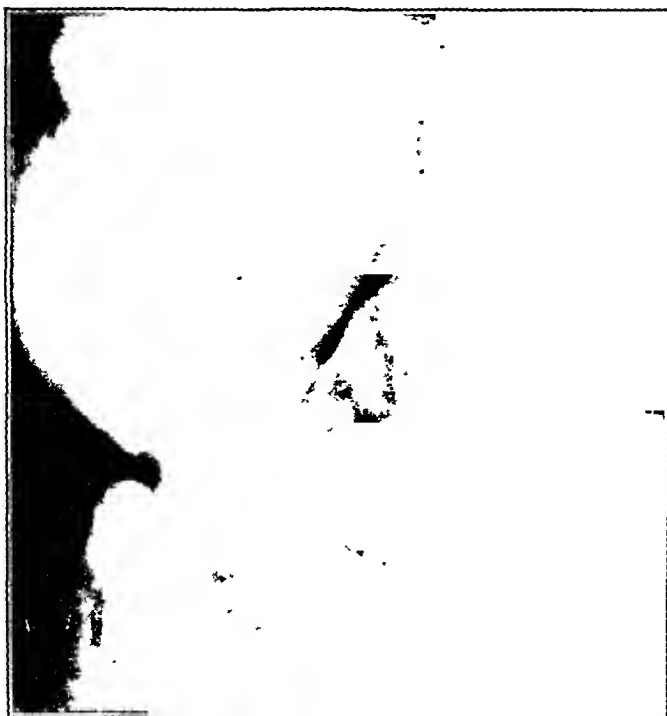


Fig. 4.—Case 2. Barium enema 300 days after streptomycin started shows a normal, well filled cecum.

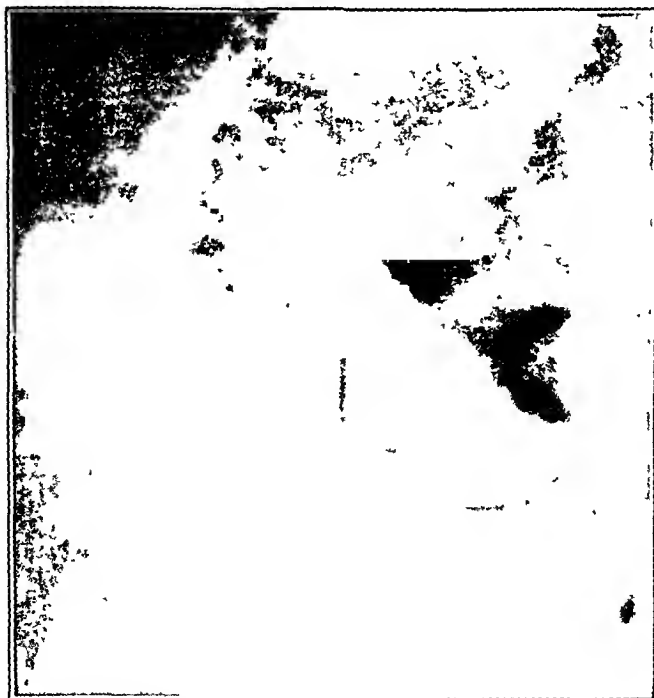


Fig. 5.—Case 3. A film taken 6 hours after ingestion of barium meal 12 days before streptomycin was started shows marked irregularity in terminal ileum and cecum.

double contrast barium enema showed a completely normal colon (Fig. 4).

Case 3. He received 60 days' intramuscular treatment of 1.8 gm. per day after 4 months of symptoms. At 88 days before streptomycin, the barium enema showed an irregular, poorly filled cecum. At 49 days before treatment, on gastro-intestinal series, the cecum and ascending colon showed rapid passage of barium. At 12 days before treatment, there was marked irregularity in terminal ileum and cecum with head of barium column in sigmoid at 6 hours (Fig. 5). After 30 days of streptomycin, the contrast meal showed a narrow, irregular mucosal pattern in terminal ileum and an irregular spastic cecum. After 40 days of treatments, the barium enema showed a "feathery" irregularity of cecum especially at ileo-cecal juncture, and absence of the spasticity previously seen. At 86 days after streptomycin the enema study show-

ed no deformity or irregularity in colon or terminal ileum, and good filling of both. At 300 days after streptomycin the gastro-intestinal series was normal (Fig. 6).

Case 4. He received 120 days' intramuscular treatment of 1.8 gm. per day, after 22 months of symptoms. At 60 days before streptomycin the gastro-intestinal series showed a markedly irregular and narrowing cecum. These findings persisted after 120 and 180 days after streptomycin, in spite of complete relief of symptoms in 2 weeks and reduction of stools from 4 to 1 per day.

Case 5. He received 120 days' intramuscular treatment of 1.8 gm. per day, after 5 months of symptoms. At 20 days before streptomycin, the gastro-intestinal series showed an extensive, spastic filling defect of cecum and ascending colon, persistent throughout the series (Fig. 7). At 50 days after streptomycin, the barium enema was interpreted as showing a normal intestinal pattern (Fig. 8).



Fig. 6.—Case 3. A film taken 6 hours after ingestion of barium meal 300 days after the start of streptomycin shows a normal cecum and ascending colon.



Fig. 7.—Case 5. A film taken 7 hours after ingestion of barium 20 days before streptomycin was started shows an extensive spastic filling defect of cecum and ascending colon.



Fig. 8.—Case 5. A barium enema taken 50 days after the start of streptomycin was interpreted as showing a normal intestinal pattern.

Case 6. He received 60 days' intramuscular treatment of 2 gm. per day, after 5 months of symptoms. At 12 days before streptomycin, the gastro-intestinal series showed: cecum and ascending colon tubular almost to hepatic flexure with complete loss of haustral markings and numerous very fine irregularities. At 59 days after streptomycin, the films showed slight widening of lumen of ascending colon and a return of haustral

spastic. At 60 days after streptomycin the gastro-intestinal series showed an irregularity only in the region of the ileo-cecal valve. At 120 days after streptomycin the enema showed further improvement, no irregularity and better cecal filling.

Case 8. He received 120 days' intramuscular treatment of 2 gm. per day, after 32 months of symptoms. At 30 days before streptomycin the barium enema showed a 5 cm. segment just distal to

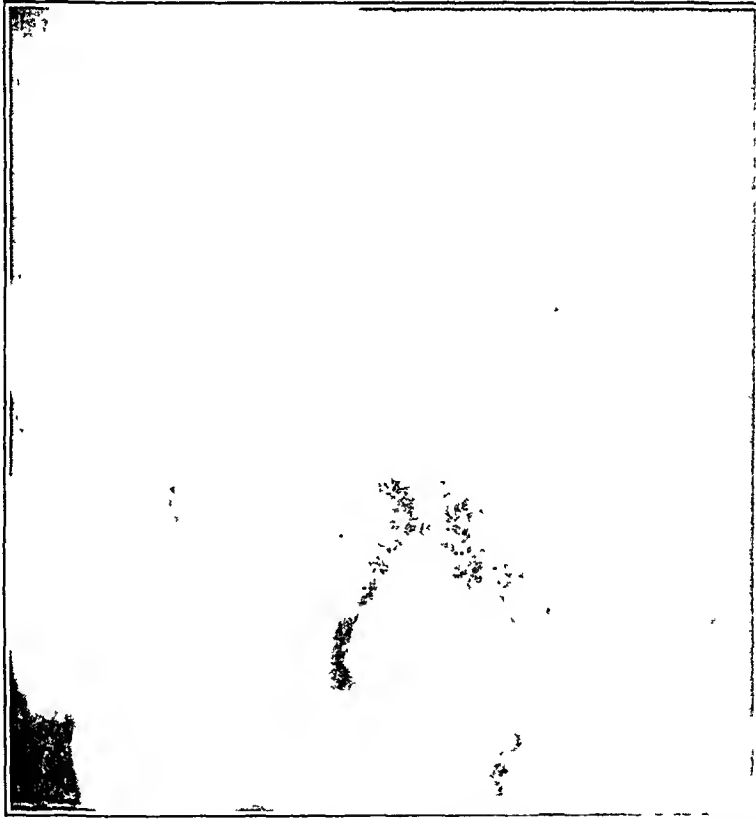


Fig. 9.—Case 31. A film taken 6 hours after ingestion of barium 14 days before streptomycin was started shows irregularity of mucosal pattern, defective filling, spasm and ulceration of cecum and ascending colon, dilated terminal ileum and swollen ileo-cecal valves with a string-like terminal ileum.

markings. Fine irregularities persisted and the cecum did not fill. At 120 days there was "further improvement but still not normal."

Case 7. He received 60 days' intramuscular treatment of 2 gm. per day, after 6 months of symptoms. At 18 days before streptomycin, the gastro-intestinal series showed an irregular spastic cecum and proximal ascending colon. At 13 days before treatment, the enema also showed same area moth-eaten, irregular,

splenic flexure narrowed to one-third and irregular contour at the splenic flexure, and proximal to the splenic flexure a 4 cm. segment of normal colon. The balance of transverse, ascending colon and cecum were devoid of haustration, and narrowed to  $\frac{1}{3}$  and shortened. There was a spotty mucosal pattern typical of ulceration. A post-evacuation film showed  $3\frac{1}{2}$  cm. of ileum as a "string sign." At 25 days before treatment the gastro-intestinal series showed the same, with all but the distal

descending colon involved in the ulcerative process. There was a small gastric residue at 6 hours with most of the barium in the ileum and colon. At 30 days after streptomycin, the barium enema showed a definitely lessening spasticity with easy filling of terminal ileum, the distal several feet of which seemed to be involved. At 82 days after streptomycin, the enema showed spasm and narrowing further diminished for most of the bowel, and the ulcerative pattern was absent. The ascending colon,

continual narrowing. Several diverticula were present on the lateral wall of the ascending colon at the level of the ileocecal junction. There was a narrow terminal ileum, with definite dilatation in several coils of ileum. At 150 days after streptomycin the series showed the stomach empty at 6 hours and the head of the meal in the distal colon.

Case 10. He received 14 days' intramuscular treatment of 2 gm. per day, after 5 months of symptoms. At 12 days



Fig. 10.—Case 31. A film taken 6 hours after ingestion of barium 60 days after streptomycin was started shows a normal cecum and terminal ileum.

however, was narrower and shortened as compared to previous films. Post-evacuation films showed less spasm in the ascending colon than at previous examination. At 91 days after streptomycin the series showed at 4 hours a "string-like" loop of ileum at level of 15. There was normal intestinal motility, but a bizarre distortion of the terminal ileum and proximal colon. At 150 days after streptomycin the barium enema showed further shortening of cecum and ascending colon, with

before streptomycin, the 4 hour gastro-intestinal film showed the barium head in the rectum. The cecum and terminal few centimeters of ileum were ragged. At 21 days after streptomycin, there was marked improvement of the cecal deformity.

Case 11. He received 14 days' intramuscular treatment of 2 gm. per day, after 14 months of symptoms. Before treatment the barium enema showed changes in the cecum and terminal ileum

and a fistulous tract from the medial aspect of the ascending colon just above the ileocecal valve. At 14 days after streptomycin, there was slight, but definite improvement in cecum and fistulous tract, represented by only a small out-punching at its previous site.

Case 18. He received 68 days' intramuscular treatment of 1 gm. per day after 4 months of symptoms. At 12 days before streptomycin, the gastro-intestinal series showed possible ulceration in the terminal ileum, slight hypermotility, and spasm in the terminal ileum. At 30 days after streptomycin, the series showed a normal pattern and motility.

Case 21. He received 14 days' oral treatment of 2 gm. per day, after 7 months of symptoms. At 30 days before streptomycin, the gastro-intestinal series showed a suggestive filling defect in the ileo-cecal region. At 17 days before treatment, the barium enema showed a constant filling defect in the region of the ileocecal valve; tentative diagnosis, tuberculous enteritis. At 14 days after streptomycin, a 14 ASM flat plate showed distended loops of bowel with fluid levels; the enema showed normal filling of the large bowel, and a small bowel obstruction.

Case 23. He received 120 days' oral treatment with 2 gm. per day, after 4 months of symptoms. At 60 days before streptomycin, the gastro-intestinal series showed a spastic cecum. At 20 days before treatment, the barium enema showed a markedly spastic cecum that could not be filled. At 155 days after streptomycin there was no roentgenologic evidence of disease.

Case 24. He received 30 days' intramuscular treatment of 2 gm. per day. During 45 days he got no treatment because of the appearance of toxicity, and then 30 days' intramuscular treatment was given: 1 gm. per day. A tuberculous appendix was removed 2 months previous to streptomycin. The duration of symptoms is not known. At 25 days before treatment, the gastro-intestinal series showed an irregularity of the distal 5 cm. of the terminal ileum and some spastic irregularity of the cecum. At 41 days

after streptomycin the series showed the region of cecum and ileo-cecal valves much better filled and smoother. At 75 days after streptomycin, the series showed the cecum well rounded and filled, and the pattern of the small bowel in vicinity of the ileo-cecal valve more nearly normal.

Case 25. He received 60 days' intramuscular treatment of 2 gm. per day, after 3 months of symptoms. At 40 days before streptomycin, the gastro-intestinal series showed a contracted irregular cecum and lower portion of ascending colon. At 30 days after streptomycin, the series showed better filling, slight persistent irregularity, and considerable improvement.

Case 26. He received 14 days' oral treatment of 2 gm. per day, 107 days' intramuscular treatment of 1 gm. per day, after 4 months of symptoms. At 11 days before streptomycin the 6-hour film showed some gastric retention, with the head of barium at the ileo-cecal valve. There was slight distortion of the cecum, suggestive of ulceration. At 10 days before treatment, the barium enema showed a deformity of the cecum, possibly due to ulceration. At 30 days after streptomycin the gastro-intestinal series was normal. At 74 days after streptomycin, the 6-hour film showed no gastric retention, and the head of barium was in cecum. There was some constriction in the last part of the ileum, suggestive of spasm.

Case 30. He received 85 days' intramuscular treatment of 2 gm. per day, after 2 months of symptoms. At 8 days before streptomycin, the barium enema showed the terminal ileum markedly contracted, questionable contraction of cecum. At 4 days before treatment, the series showed moderate spasticity of the transverse colon, and descending colon, induration and spasm of the terminal ileum. At 27 days after streptomycin the terminal ileum had a wider lumen and less irritability. At 62 days after streptomycin the series showed residual narrowing of the terminal ileum, more than on previous examination, suggestive of scarring but with no sign of activity of the ulcerative disease.

Discussion. A co-operative study involving 15 hospitals, a much larger



group of doctors and uncounted numbers of nurses, secretaries, technicians and other hospital personnel has been summarized by the authors at the request of the Veterans Administration's Central Office Committee on Streptomycin. The intricacy of the program together with its novelty has made it difficult to assemble information which could be easily handled statistically. Fortunately, however, the beneficial effect of streptomycin on ulcerating tuberculous enterocolitis secondary to pulmonary tuberculosis is so apparent

clinically and by Roentgen-ray that detailed analyses of subtle changes is unnecessary. The use of streptomycin completely alters, for the first time in the history of tuberculosis, the dread outlook of "phthisical persons who develop diarrhea."

**Summary:** Thirty-three patients suffering from active pulmonary tuberculosis and a complicating tuberculous enteritis have been treated with streptomycin with striking improvement in all manifestations of the intestinal disease.

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# AN IMPROVED METHOD FOR THE DETECTION OF OSMOTIC ABNORMALITIES OF ERYTHROCYTES

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THE usual clinical fragility test with hypotonic salt solutions leaves much to be desired. It is time-consuming and the results obtained with it are not always reproducible. Both of these defects have their origin in the circumstance that it involves a condition of osmotic and diffusion equilibrium. This requires some time for its attainment and it is strongly influenced by factors such as temperature, pH, etc.<sup>7,8</sup>

The present method\* depends upon the measurement of rates rather than final equilibria; it is therefore more rapid than the usual method. Instead of an hour or more for the completion of a test, an observation time of 3 minutes suffices. Instead of a series of hemolytic solutions, only a single solution is needed. The amount of blood required is very small, a few drops from a finger usually being sufficient. The results are satisfactorily reproducible and they furnish more varied and more complete information than do those of the older method. Finally, a permanent record can be obtained which not only shows the chief peculiarities of the blood at a glance but provides quantitative data for more exact analysis at any time.

**Standard Method.** By this method the course of hemolysis is followed photographically in a solution of a penetrating substance such as thiourea or glycerol suitably modified by the addition of a small known amount of sodium chloride. The time of hemolysis of a given red cell in such a solution depends in

part on its permeability to the chosen solute and in part on the degree of swelling it will tolerate before undergoing hemolysis, i.e., its fragility in the usual sense. From a purely theoretical point of view it might seem undesirable to combine the 2 dissimilar cellular properties of permeability and fragility. Practically, however, it is advantageous in that it provides a greater number of possibilities for the distinction of abnormal from normal cells. Since the number of penetrating solutes is very large, and since the osmotic effect of the added salt may be varied over a wide range, the experimenter has at his disposal an almost unlimited number of possible test solutions from which he may select the one best suited to his needs.

Of the solutions so far investigated, the 2 most generally useful are 0.24 M thiourea and 0.18 M glycerol, the former containing 0.18 and the latter 0.36 gm. % of sodium chloride. Within certain limits, the greater the amount of salt the greater will be the visible effect of any highly resistant cells that may happen to be present. Increasing the pH of the solution has much the same effect as increasing its salt concentration.

The fact that the hemolytic test solution contains at least one-fifth of the isotonic concentration of sodium chloride has an important practical advantage, namely that the erythrocytes to be examined may be collected in a buffered 0.9% solution of sodium chloride, which is then automatically diluted to the proper extent (e.g., 1 part of erythrocyte suspension to 4 parts of pure 0.3 M thiourea or to 1 part of 0.9% NaCl plus 3 parts of 0.3 M glycerol) at the time the test is made. In this way a very small amount of blood suffices for the test, no anticoagulant is needed, the pH is kept under control at all times, mixing by pouring the hemolytic solution into the suspension occurs in a reproducible way, and exact measurements of all volumes

\* A brief note concerning this method appeared in the Proceedings of the Philadelphia Physiological Society for 1916-17 (*Am. J. Med. Sci.*, 212, 756, 1916).

can be made with ordinary volumetric pipettes

In the preparation of the necessary solutions sodium chloride which is free from silver<sup>1,12</sup> (e.g., Merck's "reagent, for biological use") and glycerol and thiourea of the best quality should be employed. Since the permeability of human erythrocytes to glycerol and their rate of hemolysis in glycerol solutions are greatly decreased by traces of copper,<sup>5,6</sup> it is essential in work with this solute to use copper-free distilled water for all solutions.

For the maintenance of a pH value of approximately 7.4 (except when otherwise desired) the blood is collected directly in 0.9% NaCl buffered 1 in 20 with an isotonic phosphate mixture having this reaction, the subsequent changes caused by dilution are reasonably constant from experiment to experiment. A phosphate solution which at pH 7.4 is very nearly isosmotic with blood may be prepared by adding concentrated HCl drop by drop to M/8  $\text{Na}_2\text{HPO}_4$  until the desired pH is attained. This stock solution keeps well in the refrigerator, but its dilute mixture in NaCl does not, and should therefore be freshly prepared at frequent intervals.

If a known volume of blood is collected with a syringe from a vein without stasis, it is sometimes advantageous to dilute it exactly 25 times with the buffered salt solution, after a further ten-fold dilution its hemoglobin value can then be determined by direct comparison with the frequently-employed acid hematin or hemoglobin standards for a 250-fold dilution of blood. For hemolysis tests alone, however, an entirely adequate blood suspension can be prepared from a few drops of finger blood without exact measurement, care merely being taken to keep its concentration below the point at which coagulation is possible. In cases of severe anemia, in order to obtain a sufficiently concentrated suspension, it is sometimes necessary to add a trace of heparin to the buffered salt solution or to centrifuge a more dilute suspension. For further study the initial suspension in all cases is brought to a chosen optical density, either accurately with a Klett-Summerson photoelectric colorimeter, using the red filter, or approximately by the procedure described below. It is then ready for use.

While immediate examination of a sample of blood is desirable, properly prepared initial suspensions may be kept for a time in a refrigerator. Normal blood under these conditions preserves its properties fairly well for

several days, some kinds of abnormal blood change more rapidly, but are nearly always usable for 12 hours or more. When blood is so kept, it is of course necessary to adjust its temperature before using it for a test. Proper temperature control is very important, particularly when an accurate quantitative analysis of the thiourea hemolysis curves is desired. In our own work a temperature of 24° C has been found to be a convenient compromise between winter and summer room temperatures.

The properties of the entire erythrocyte population of the blood are best shown by means of a photographic hemolysis curve. The apparatus employed for this purpose is a modification of that first suggested independently by Parpart<sup>11</sup> and by Orskov.<sup>10</sup> Our own form of it employs as a very constant source of light, a Mazda No. 1183 50 candle power bulb operated by 6 Exide 7-plate chloride type storage cells arranged as a series of 3 parallel pairs. The light passes through the suspension of hemolyzing cells contained in a tube in a water bath to a Weston No. 594 photronic cell. A very sensitive and rapid Kipp and Zonen micro-galvanometer, an appropriate light projector, and a Cambridge recording camera, suitably slowed by gears, complete the equipment.

A useful form of record (Figs. 1 and 2) is one in which exposures are made every 10 seconds for exactly 3 minutes. At the beginning of each record there is indicated the position of no hemolysis, and at its end that of complete hemolysis, the necessary standards being obtained by appropriate dilutions of the working suspension with isotonic salt solution and saponin-containing distilled water, respectively.

**Results.** Figs. 1 and 2 will serve to illustrate the general nature of the results yielded by the method†; further applications to clinical problems will be discussed by several of our associates.<sup>2</sup> The first 2 records in Fig. 1 are "normal" thiourea curves; with mi-

† Grateful acknowledgment is made to all the persons, too numerous to mention individually, who assisted us in obtaining samples of abnormal blood with accompanying diagnoses and clinical data, or who furnished their own blood for the establishment of the normal range of variation.

nor modifications they would represent the behavior of almost all of our series of over 200 healthy white subjects of both sexes. The corresponding curves for Negroes tend—though with exceptions—to rise more slowly than those for whites.<sup>2,4</sup> The chief features of a “normal” thiourea curve at a temperature of 24° C. and a pH value of 7.4 are: (a) an initial slow rise occupying a time of from a little less than a minute to 70 seconds, or occasionally more, (b) a sudden acceleration of the rise,

marked by the appearance of a more or less distinct “angle” where the slope of the curve abruptly changes, (c) a rapid rise lasting perhaps 50 to 70 seconds, and (d) a final slow rise which virtually ceases long enough before the end of 3 minutes to give a flat top to the curve at or near the level of complete hemolysis.

It is easy to show that the initial slow rise is due to swelling of the cells with little hemolysis. It is only necessary at the end of any selected time to add

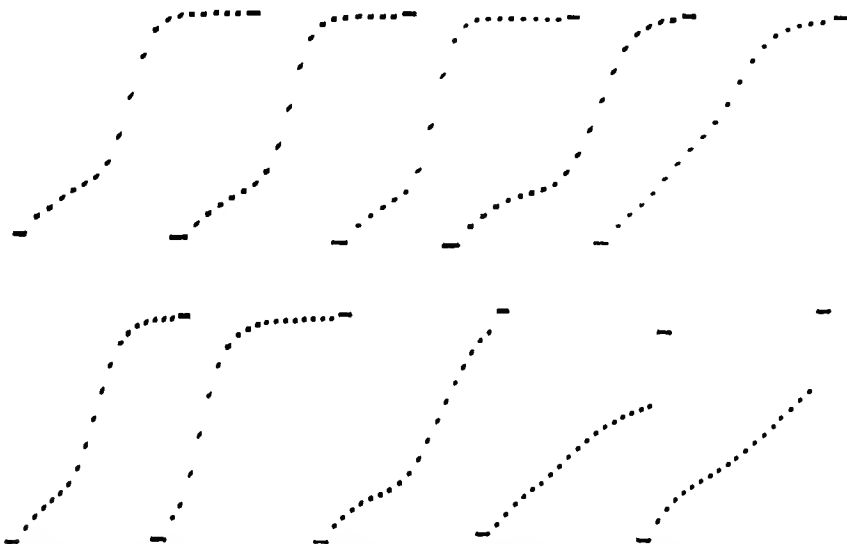


FIG. 1.—Hemolysis in a mixture of 4 parts of 0.3 M thiourea and 1 part of 0.9% NaCl. Photographic recording for 3 minutes at 10 second intervals. Ordinates represent the extent of swelling and hemolysis; abscissae, time. Slight differences in the speed of the camera do not prevent accurate comparisons, since each record carries its own time scale.

Above (from left to right): (a) a typical white normal individual, (b) a second typical normal, (c) an apparently normal individual in whom a slightly increased fragility has been regularly demonstrable for almost 5 years, (d) a somewhat resistant normal, (e) bank blood after storage for 3 weeks.

Below (from left to right): (f) nutritional anemia, (g) hemolytic anemia, (h) primary pernicious anemia, (i) sickle cell anemia, (j) carcinoma of the cecum.

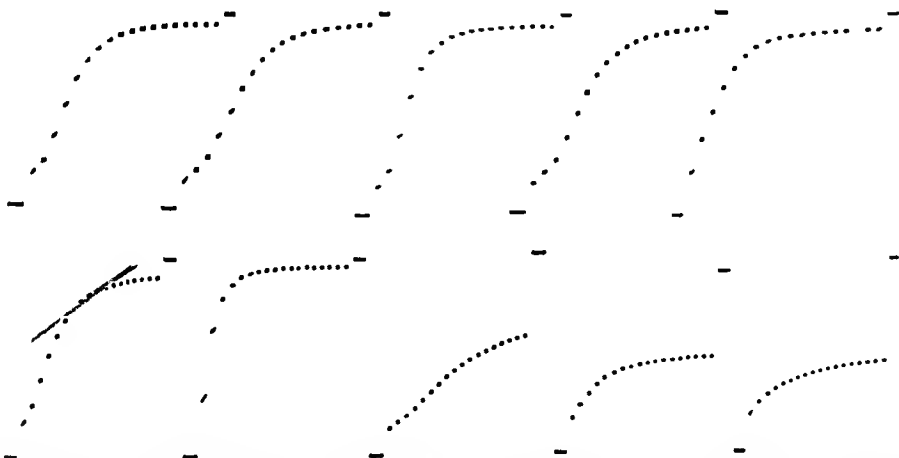


FIG. 2.—Hemolysis in a mixture of 3 parts of 0.3 M glycerol and 2 parts of 0.9% NaCl. The curves present the same samples of blood as in Fig. 1, arranged in the same order, and similarly recorded.

enough concentrated sodium chloride to the tube containing the cells (*i. e.*, 0.6 ml. of 30% NaCl to 25 ml. of suspension) to bring the total concentration of NaCl to approximately 0.9%. Hemolysis is thereby stopped and the contents of the tube may now be centrifuged and its hemoglobin content determined. It is rare with the blood of healthy persons under these conditions to find any very considerable amount of free hemoglobin in less than one minute. Above the "angle" of the curve the amount of hemoglobin so found increases rapidly. The characteristically steep slope of the curve in this region is due to the fact that in normal blood most of the erythrocytes have fairly similar osmotic properties and undergo hemolysis at nearly the same time, with only a few of the most resistant cells remaining to account for the final slow leveling off of the curve.

The presence of abnormally fragile cells is clearly indicated by a shortening of the time required to reach the "angle", which in extreme cases may even fail to appear at all. A good example of this condition is shown in Fig. 1g representing blood from a case of hemolytic anemia. The rapid rise of the curve and the absence of any "angle" are obvious at a glance. We have also observed the gradual disappearance of the "angle" in bank blood tested at intervals over a period of several weeks (Fig. 1e).

The opposite abnormality of extremely high osmotic resistance of at least some of the cells is illustrated in Figs. 1h, 1i, and 1j, representing pernicious anemia, sickle-cell anemia, and

carcinoma of the cecum, respectively. Not only is the rise of the curve slower and more uniform here than in the case of normal blood but the level attained in 3 minutes is much lower. Sometimes in such cases the curve is convex above, sometimes it is concave, and sometimes it approaches a straight line. A further analysis of such differences, either with or without changes in the amounts of NaCl added to the hemolytic solutions, may perhaps yield additional information of value.

We have made many comparisons of hemolysis curves such as those in Fig. 1 with fragility determinations of the usual sort and have never failed to find a general parallel in the results.† The present method, however, yields much more detailed and reproducible information than the older one, does so in a much shorter time, and requires only a single solution for cells having all possible degrees of susceptibility to osmotic hemolysis from the most extreme fragility to the most extreme resistance. The reproducibility of the results is well shown by repeated observations on the blood of a single individual. It happens that one of the authors, who is in good health as far as is known and has a normal hemoglobin value, has erythrocytes that are noticeably though not very strikingly more fragile than those of most other normal subjects, the difference with hypotonic salt solutions amounting to a few hundredths of 1% of sodium chloride. During a period of nearly 5 years he has had occasion to obtain dozens of curves similar to Fig. 1c. Over this entire period the "angle" of his thiourea curve has

† For the accurate measurement of fragility with hypotonic salt solutions the following method has been found to be both reliable and convenient. Two stock solutions are required (a) 1 part of 0.9% NaCl to 3 parts of distilled water and (b) 2 parts of 0.9% NaCl to 3 of water. When 4 parts of solution (a) are poured into 1 part of the adjusted buffered cell suspension, the cells are thereby almost instantaneously exposed to 0.36% NaCl. When solution (b) is similarly employed, the corresponding concentration is 0.17% NaCl. Under these conditions at 24° normal erythrocytes at the end of 3 minutes show almost but not quite complete hemolysis in the former and a very slight degree of hemolysis in the latter solution. The 2 solutions together, therefore, serve to demonstrate with considerable quantitative exactness the presence of abnormally resistant and abnormally fragile cells, respectively. The necessary measurements may be made either on the hemoglobin content of the external liquid or on the optical density of the suspension itself. In the latter case it should be remembered that an increased transmission of light may be caused by a swelling of the cells as well as by hemolysis.

never failed to appear about 10 seconds earlier than that of most other normal thiourea curves. On the other hand, an apparently equally healthy colleague for more than a year has shown an equally constant shift of his "angle" by some 20 seconds in the opposite direction. In abnormal bloods such individual differences are much more striking, and have been found in many cases to be equally reproducible from day to day.

For some purposes the glycerol-NaCl solution mentioned above has proved to be useful. In general, it emphasizes more strongly than does the thiourea solution the presence of cells of very high osmotic resistance, since it contains enough salt (0.36% after mixing with the cell suspension) to prevent completely the hemolysis of such cells. On the whole, the results obtained with this solution have been especially instructive in cases of pernicious anemia and carcinoma of the gastro-intestinal tract (compare for example Figs. 1 and 2 in which the same individuals are represented). In view of the finding of Dziemian<sup>3</sup> that in the rabbit the permeability of reticulocytes to glycerol is enormously greater than that of mature erythrocytes, it will be interesting to observe with care the form of the glycerol curves of human subjects having high reticulocyte counts.

Colorimeter method. When the necessary equipment for the standard method is not available, much the same type of information can be obtained with the same solutions and blood suspensions in several other ways, though without the advantages of photographic recording. One method is to use a Klett-Summerson photoelectric colorimeter for following the course of hemolysis. Unfortunately, direct observations of hemolyzing erythrocytes with this instrument fail to bring out differences between normal and abnormal bloods as clearly as does the standard method, which has a greater relative sensitivity in the important upper part of the hemolysis curve. Accurate temperature control of a tube in the colorimeter is also difficult, and there is an appreciable lag in fol-

lowing rapid optical changes. Despite these difficulties, however, any considerable osmotic abnormalities of erythrocytes can readily be detected by this method.

For greater accuracy it is sometimes advantageous to carry on the process of hemolysis at a constant temperature outside the instrument and then to stop it at selected points by the sudden addition of a sufficient amount of very concentrated sodium chloride to bring the concentration of the entire mixture to 0.9%. Accurate leisurely readings of the suspension may then be made with the red filter, or of its free hemoglobin, after centrifuging, with the green filter. A time of 1 minute with the thiourea mixture is suitable for showing in this way the presence of abnormally fragile (or permeable) cells; a time of 3 minutes that of abnormally resistant ones.

Slit method. At times it may be desirable with no apparatus but a few test tubes to examine a sample of blood for indications of the nature and approximate magnitude of its possible departure from osmotic normality. This can be done as follows: A reasonably constant source of light is first provided by making a small slit (*e.g.*, 1 x 25 mm) in a piece of blackened cardboard, pasting a piece of tissue paper over its rear surface, and placing behind it a suitable electric light bulb. The time is then measured at which the slit just becomes visible when viewed through a hemolyzing suspension in a 25 x 200 mm. test tube, the tube being held close to the eye and gently rocked from side to side.

Since it is presumed that no instrument is available for the standardization of the working suspension, this is done by eye. First 0.5 ml. of the original concentrated suspension is placed in a clean test tube of the dimensions mentioned, then unbuffered 0.9% NaCl is added until the slit just becomes visible when viewed through the contents of the tube. A mark is made on the tube at the top level of the diluted suspension and the latter is poured into another similar tube for reference later, if needed. Next 10 ml. of the original suspension is placed in the marked tube and buffered NaCl is added to the mark, thus giving a suspension 20 times as concentrated as that through which the slit can just be seen. When this suspension is diluted 5 times and is then allowed to undergo hemolysis, the slit should again be seen when three-quarters of the cells have disappeared.

Though this approximate method of calculation neglects the optical effects of free hemoglobin and of swelling of the unhemolyzed cells, it nevertheless leads to a very satisfactorily reproducible end-point, even in the hands of different observers at different times.

The "slit time" for approximately 75% hemolysis with normal blood in the thiourea solution is usually of the order of 2 minutes at 24° C.; with very fragile erythrocytes it may fall below 1 minute and with highly resistant ones it may rise as high as 10 minutes, or even more. It frequently happens that the differences between normal and abnormal blood are more conspicuous at slit times representing more than 75% hemolysis. In such cases the working suspension can be made more than 20 times as concentrated as the one through which the slit is just visible. It is also sometimes advantageous in working with this method to exaggerate the effect of highly resistant cells by increasing the amount of salt in the hemolytic solution. The necessary details of this and other procedures will readily suggest themselves in practice.

**Electrocardiograph method.** This method, developed by our associates W. E. Love, R. E. Edelberg, and E. F. MacNichol, combines the desirable features of the standard method, including photographic recording, with greater availability and compactness of equipment.

Records obtained with it will appear in the following paper by Dickstein *et al.*<sup>2</sup>, and it will be described in detail elsewhere<sup>3</sup>.

**Summary.** In order to avoid certain sources of error in the usual clinical fragility test with hypotonic salt solutions, as well as to shorten the time and reduce the number of solutions required for a test, an alternative procedure is suggested in which a continuous hemolysis curve is obtained, either with or without photographic recording, in a solution containing a penetrating solute such as thiourea or glycerol.

The hemolysis curves of more than 200 normal subjects obtained in this way have shown a very satisfactory degree of similarity and reproducibility. Small individual peculiarities, when present, may reappear with constancy over a period as long as 4 years.

Characteristic and easily recognizable departures from normality have regularly been found in certain of the blood dyscrasias. Evidences of abnormal fragility and abnormal resistance shown by the hemolysis curves, in general, run parallel with those obtained with hypotonic salt solutions, but the new method brings out more detailed differences and yields more reliable results than the older one.

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# THE OSMOTIC RESISTANCE OF HUMAN ERYTHROCYTES IN NORMAL, CARRIER AND ANEMIC STATES:

With Special Reference to Changes Due  
to Age, Race, Sickle-cell Anemia,  
Mediterranean (Cooley's) Anemia and Congenital  
Hemolytic Icterus.

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ABNORMALITIES of the osmotic resistance of erythrocytes in various blood disturbances have been recognized for many years and are frequently looked for as an aid in diagnosis. The usual fragility test, which employs hypotonic salt solutions, is not always satisfactory, and its uncritical use has led to many contradictory statements in the literature. One of the most frequent sources of error in the test, as ordinarily performed, is the failure to control such critical variables as pH and temperature. Jacobs and Parpart<sup>19</sup> have shown that a temperature change of 0.5° C. or a pH change of 0.05 units has a measurable effect on the osmotic resistance of erythrocytes. Additional factors frequently neglected are oxygenation, relative proportions of cells and solutions, manner of mixing, and duration of exposure.

Jacobs and his associates<sup>18</sup> have recently developed a method which largely eliminates these various sources of error, and which has been found to give reproducible results over a period of years. This method, adapted for photographic recording with a port-

able electrocardiograph as suggested by Love, Edelberg, and MacNichol,<sup>20</sup> has been used in the present study. The hemolytic solutions employed were those recommended by Jacobs, namely: (1) 0.18M glycerol in 0.36% NaCl, (2) 0.24M thiourea in 0.18% NaCl, (3) 0.47% NaCl, and (4) 0.36% NaCl. Each solution has its own particular usefulness, as will appear later.

**Procedure.** The blood for the test is collected directly into a small test tube containing 0.9% NaCl solution buffered to pH 7.4 with an isotonic phosphate buffer. Eight drops of finger blood usually suffice. Collection from a finger rather than from a vein enhances the value of this test in pediatric practice. The suspension so obtained is then diluted with more of the buffered salt solution to a chosen optical density as measured with a Klett-Summerson photoelectric colorimeter, using the red filter. Oxygenation is virtually complete in such suspensions. One part of this suspension and 4 parts of the hemolytic solution are then separately brought to  $24 \pm 0.5^\circ \text{C}$ . After sudden mixing, the changes in light transmission which accompany the swelling and hemolysis of the cells are recorded



photographically for 3 minutes at a constant temperature of 24°C.\*

Figure 1 shows a set of typical curves obtained from the blood of a normal white adult, using the 4 hemolytic solutions. Each record shows, first, the deflection produced by a non-hemolyzed suspension of the cells being studied. Following a depressed signal point, the course of swelling and hemolysis is shown at 6 second intervals for 3 minutes. Finally, following another signal point, the deflection of a completely hemolyzed solution is shown.

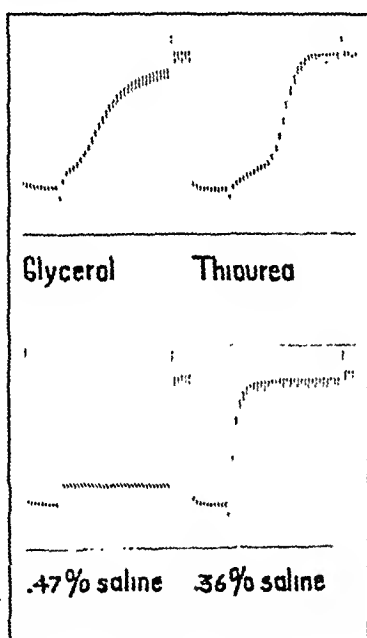


Fig. 1.—Records obtained from a typical white normal with the solutions indicated. Ordinates indicate swelling and hemolysis of the erythrocytes; abscissae indicate time, recorded at 6 second intervals. A record of 0% hemolysis and 100% hemolysis is indicated before and after each curve. See text for details.

For the purpose of analysis, the amount of rise at the end of a 3-minute period is compared with that corresponding to complete hemolysis, and the ratio is expressed as a percent of the maximum deflection. Although the percent deflection does not equal numerically the percent hemolysis,

it is related to the latter in a reproducible manner; the greater the percent deflection the greater the fragility of the cells. It should be noted that small deflections may be produced by swelling alone without hemolysis.

**Results.** Having available a delicate method which gives reproducible results, it has seemed worth while to re-investigate the osmotic behaviour of normal erythrocytes, and of those found in several types of anemia. This study comprises observations on 170 normal and 90 abnormal individuals. The normal group was composed of healthy individuals free from anemia. Each abnormal case was diagnosed on the basis of clinical and laboratory findings other than the fragility test. No individual with a questionable diagnosis was included. All samples of blood were obtained by the method described, and tested with the 4 hemolytic solutions within 6 hours of collection. All data except those for 0.47% NaCl appear in Table 1. Results of hemolysis with the latter solution have not been found to be abnormal in any condition tested except in congenital hemolytic icterus, in which the fragility is increased. Figures 5 and 6 show typical photographic records for each abnormality to be discussed.

**Children vs. adults.** It has not generally been recognized by clinicians that there may be a marked difference between the osmotic resistance of the erythrocytes of adults and children. One worker<sup>3</sup> finds no difference; another<sup>14</sup> notes that children are "slightly more resistant."

The infants and children studied were from a boarding school and from the surgical wards of The Children's Hospital of Philadelphia (those admitted for elective surgery, uncomplicated by blood disorders). Medical students.

\*The recordings were made in the Department of Physiology, Medical School, University of Pennsylvania, and were facilitated by a grant to Professor M. H. Jacobs.

nurses, and other persons associated with the Medical School of the University of Pennsylvania were used as normal adults. In all subjects hemoglobin determinations were made<sup>13</sup> and only persons showing normal values were included. The moist non-stasis sickling test<sup>12</sup> was performed on all Negroes and only non-sicklers were included in the normal group.

The percent deflection attained at the end of 3 minutes with each of the 3 hemolytic solutions is given in Table 1. The range and mean values are shown. It will be noted that the osmotic resistance in the white age group up to 10 years shows greater variation than that found after the 10th year, the former being more resistant on the average. This difference in the average values for the glycerol solution is shown in Figure 2. The range of values appears in full in Table 1. There appears to be little difference among

the first 6 age groups in the table with any of the solutions. In 0.36% NaCl the 63 white individuals under 10 years averaged 89.7% deflection (range 73-100) and the 62 cases over 10 years averaged 95.2% (range 90-100). Lesser differences in the same direction were noted with the thiourea solution. The difference between Negro adults and children is less marked than that among white subjects. For the proper evaluation of abnormal blood, therefore, the characteristic differences between children and adults must be taken into account.

**Whites vs. Negroes.** The red cells of the Negroes exhibit greater variation than do those of whites (Table 1), and on the whole are more resistant. This average difference between the adults of the two races is shown for the glycerol solution in Figure 2. In the 0.36% saline the Negro children averaged 78% deflection at the end of

\*The detailed data for white normal adults, from which values used in this paper have been taken, will appear in a study of carcinoma by two of the authors (Wilson and Landmesser).

TABLE 1.—SUMMARY OF OSMOTIC RESISTANCE VALUES FOR THE SUBJECTS STUDIED

	Age Range	No. of Cases	Per cent deflection after 3 minutes.					
			Mean	Glycerol Range	Mean	Thiourea Range	0.36% Saline Mean	0.36% Saline Range
Normal White	15-65 yrs.	50	91.5	80-100	99.0	94-100	95.3	90-100
Normal White	10-15 yrs.	12	90.1	80-100	99.3	98-100	95.1	90-100
Normal White	5-10 yrs.	10	80.6	62-90	96	80-100	91	73-98
Normal White	1-5 yrs.	14	84	70-95	98	96-100	94	89-98
Normal White	3-4 yrs.	7	75	62-94	97	91-100	88	80-98
Normal White	2-3 yrs.	11	71	60-82	98	96-100	87	76-99
Normal White	1-2 yrs.	8	80	70-88	96	80-100	90	85-98
Normal White	0-1 yrs.	13	73	60-90	95	88-100	87	75-100
Normal Negro	15-60 yrs.	15	71	38-88	81	52-99	76	35-92
Normal Negro	10-15 yrs.	10	66	40-92	91	64-100	76	50-96
Normal Negro	5-10 yrs.	22	72	54-90	96	78-100	84	69-98
Normal Negro	1-5 yrs.	7	58	38-90	85	50-100	67	40-96
Normal Negro	3-4 yrs.	10	72	64-92	95	90-100	84	74-96
Normal Negro	2-3 yrs.	9	69	46-86	95	80-100	79	60-94
Normal Negro	1-2 yrs.	9	49	40-74	82	65-94	64	42-84
Normal Negro	0-1 yrs.	9	64	44-88	82	60-98	80	70-95
Sickle Cell Anemia	9 mos.-14 yrs.	28	25	17-36	39	24-56	29	16-43
Sickle Cell Trait	9 mos.-11 yrs.	14	39	30-65	80	58-90	46	30-55
Cooley's Anemia	2-13 yrs.	7	46	30-56	70	52-87	55	38-70
Cooley's Carriers Adults	17-68 yrs.	12	33	23-55	79	52-98	40	28-64
Cooley's Carriers Children	2-7 yrs.	6	40	30-48	72	45-85	45	38-53

3 minutes (range 40-98) as compared with 90% for white children (range 73-100); Negro adults averaged 76% deflection at the end of 3 minutes (range 35-92) and the white adults averaged 95% (range 90-100). This difference between whites and Negroes has been suspected by a number of workers,<sup>21,26</sup> but apparently not until recently has it been clearly demonstrated<sup>17</sup> by simultaneous and exactly comparable examinations of blood from individuals of the two races.

end of the 3 minute period was 39% while that for normal Negroes of the same age group was 90%. However, in this solution the highest two of the 28 anemic individuals overlap the lowest three of the 66 normal children. Similar results were obtained with the 0.36% saline in which the anemic average was markedly lower than the normal average with a few cases overlapping. Figure 6 shows a typical record obtained with each of the 4 hemolytic solutions.

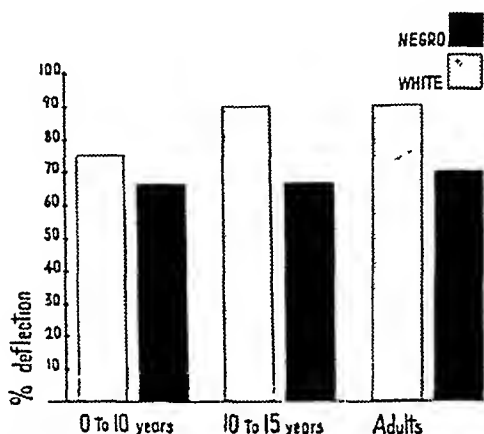


Fig. 2.—Average deflection attained in the glycerol solution for the various age groups in Negroes and whites. The higher the bar the greater the fragility.

**Sickle Cell Anemia.** There are contradictory statements in the literature as to the fragility of the red cell in sickle cell anemia. One author<sup>4</sup> claims that the fragility is increased; others<sup>9,11</sup> state that it is decreased. None of these workers mention possible racial differences in fragility, and since the race of their controls is not usually stated, it is possible that many of the latter may have been whites.

All of the 28 individuals having sickle cell anemia had a marked increase in resistance of their red cells. Shown in Figure 3 is the percent deflection in glycerol for each case. It will be noted that with this solution, there is no overlap with the normals (Table 1). With the thiourea solution the average for sickle cell anemia at the

**Sickle Cell Trait.** As with the active sickle cell anemia, reports are contradictory. One author states that the fragility is normal;<sup>6</sup> others find it decreased.<sup>11,16</sup> Here again there is a question as to the race of the controls.

It is apparent from Figure 3 that the average resistance in glycerol for the sickle cell trait lies between the values found for normal Negro children and for children with the active anemia, although a considerable overlap is found when individual cases are considered. In both thiourea and 0.36% NaCl solutions these same deviations from normal were found.

It is evident from the overlap found when individual cases are considered that osmotic resistance is not as satisfactory for differentiating the Negro

with sickle cell trait from the normal Negro as is the moist non-stasis sickling test in common use. It may be possible with a more refined sickling test to obtain a more definite correlation between osmotic resistance of the red cell and sickling. It has been noted in several instances that families with positive evidence of sickling among one or more members, contained persons with increased resistance of their red cells although the latter were negative to the sickling test.

All of our 7 cases have shown greater resistance than normal. Since the individuals with this disease were of Italian stock, 22 normal Italians were studied. No significant difference from other white normals was found. Figure 4 shows the values obtained in 0.36% saline compared with those of normal children. Using glycerol as the hemolyzing solution, the blood of patients with Cooley's anemia averaged 46% deflection (range 30-56), while the normal children averaged 75% (range 62-

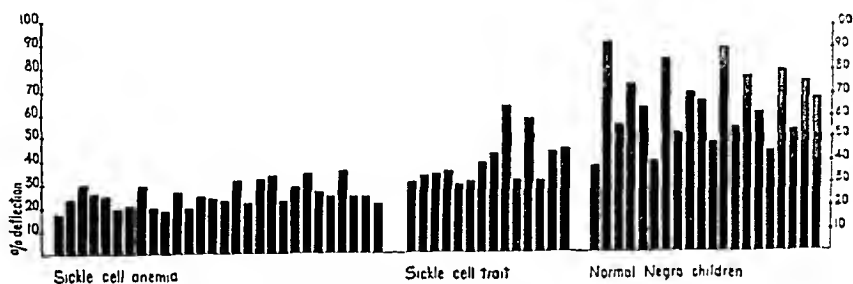


Fig. 3.—Percent deflection attained in 3 minutes with the glycerol solution. Each bar represents 1 individual. The higher the bar the greater the fragility.

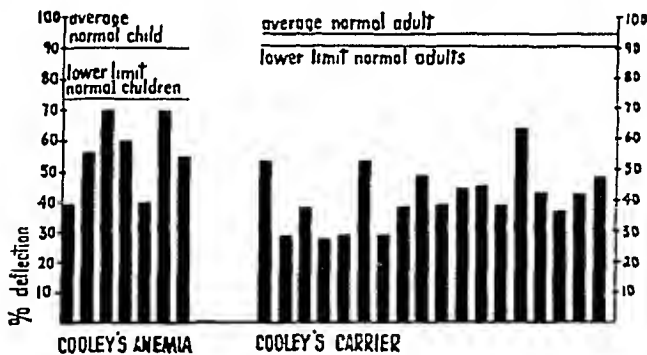


Fig. 4.—Percent deflection attained in 3 minutes with the 0.36% saline solution. Each bar represents 1 individual. The higher the bar the greater the fragility.

Mediterranean anemia (Cooley's Anemia). The high osmotic resistance of erythrocytes from children with Cooley's anemia has been noted by a number of authors.<sup>7,3,10,23,25</sup> Barrett<sup>2</sup> has demonstrated that the target cell is resistant to osmotic hemolysis. Batty, Blackfan, and Diamond<sup>3</sup> report that hemolysis begins in a more concentrated saline solution than that of the control, i.e., that some of the cells are abnormally fragile.

95). The blood in this anemia, contrary to the above report, has shown no abnormal degree of hemolysis in 0.47% saline. Since all of these cases were receiving periodic transfusions it seems likely that many normal red cells were present in the circulation. It is probable that this dilution of thalassemic cells with normal ones has given more nearly normal values than would have been the case in the untransfused patient. The 2 individuals with the most

nearly normal values had been transfused 2 weeks before testing, while the 1st, 5th and 7th cases (Fig. 4) had not been transfused more recently than 2 months earlier.

The Carrier State in Mediterranean (Cooley's) Anemia. It has been noted by several authors that the blood of persons with the carrier state of Cooley's anemia is more resistant than normal.<sup>1,5,10,23,28</sup>

The erythrocytes of all of our 18 individuals with the Cooley's carrier state were resistant and lie well below the normal range. In Figure 4 is shown

the percent deflection in 0.36% saline for each case, as well as the lower limit of normal. For simplicity, adult normals were used as controls in this group since 12 of the 18 carriers were adults. The 6 children with the carrier state fell well below the normal range for children, which is indicated in the left-hand portion of Figure 4. In the glycerol solution the blood of the adult Cooley's carrier gave values averaging 33% deflection (range 23 to 55) as compared with the normal adult average of 90% (range 80 to 100). The children showed a similar abnormality. Red

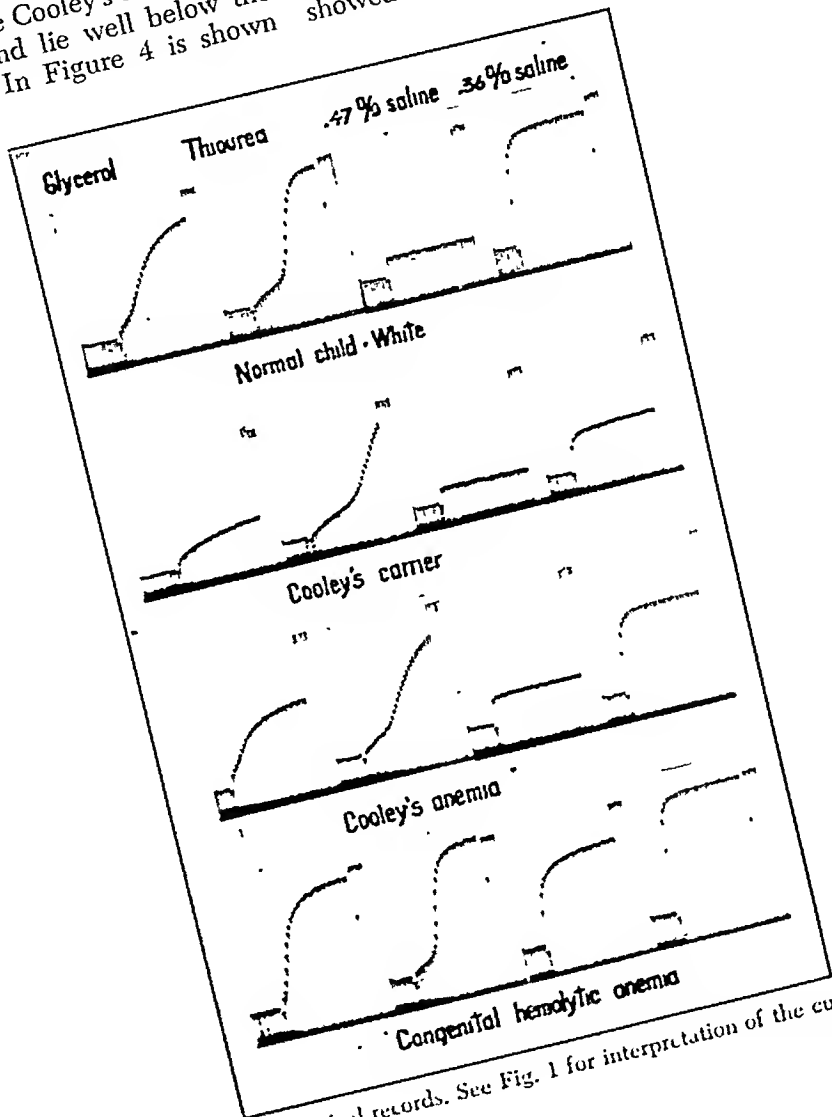


Fig. 5.—Typical records. See Fig. 1 for interpretation of the curves.

cells found in the carrier state are apparently more resistant than those in patients with active anemia, perhaps because of periodic transfusion of the latter.

The osmotic resistance test appears to be of value for the detection of both active and carrier states of Cooley's anemia, and is a valuable tool for the

of the 8 cases studied is shown in Figure 5. Both the glycerol and thiourea curves in congenital hemolytic icterus rise more rapidly than those of normal blood. The 0.47% saline curve rises to a height well above the highest normal, indicating abnormally fragile erythrocytes. It should be noted that normal cells also show a rise in this so-

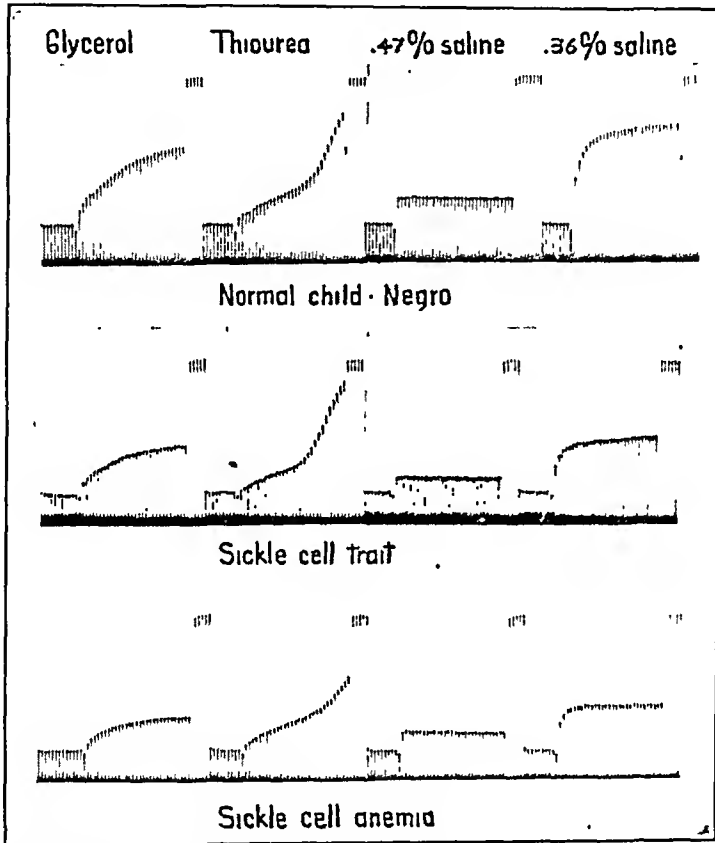


Fig. 6.—Typical records. See Fig. 1 for interpretation of the curves.

genetic study of this condition, as has been suggested.<sup>23</sup>

**Congenital Hemolytic Icterus.** The increased fragility of erythrocytes in congenital hemolytic icterus is well known. Clear cut cases may be detected with the crudest methods, but patients with slightly fragile cells may easily go unnoticed if a refined technique is not used. For the detection of fragile cells, the 0.47% saline solution has been found the most valuable. The photographic record of one

lution, though a much smaller one, due chiefly to swelling of the cells rather than to hemolysis. In 2 suspected cases of congenital hemolytic icterus this method demonstrated fragile cells which were not detected by the usual fragility test.

Among our cases is a Negro child with the typical bone changes of a chronic hemolytic anemia, microspherocytosis, a negative sickling test and markedly fragile cells. We have found 8 such cases reported in the literature to date.<sup>15,22,24,27</sup>

Miscellaneous. We have studied the bloods of 10 white and Negro children with nutritional anemia. All fell within the normal ranges for their corresponding age groups. We have followed the fragility of 1 case of proven iron deficiency anemia for a period of 4 months, before, during and after treatment, and found no significant change even 6 weeks after the hemoglobin level reached normal.

Two adults with primary pernicious anemia thus far studied showed definitely more resistant cells than normal.\* In 2 children with long standing congenital hypoplastic anemia no abnormality was noted.

Summary. 1. Utilizing a reproducible method, photographic records of the hemolysis of erythrocytes from 170 normal persons and 90 anemic individuals have been obtained.

2. In white subjects the osmotic resistance of the erythrocytes in the 0 to 10 year old age group is greater than that of normal adults. Hence,

We wish to express our gratitude to Professor M. H. Jacobs for his helpful suggestions and advice throughout the course of these experiments.

We also wish to thank Miss Grace Chen and Miss Linda C. McKoy for their technical assistance.

\*W. J. Brown and M. H. Jacobs obtained very similar results (as yet unpublished) in all of the 15 cases of this disease examined by them.

adult controls cannot be used in fragility studies in infancy and childhood. A comparable age difference was not found in the limited number of Negroes thus far examined.

3. The average osmotic resistance of the erythrocytes of the normal Negro is greater than that of the normal white in the corresponding age group.

4. The erythrocytes of children with sickle cell anemia are more resistant than those of normal Negro children. The average for individuals with the sickle cell trait lies between that for sickle cell anemia and that for the normal, but with considerable overlapping in both directions.

5. In both Mediterranean anemia and in its carrier state the blood is markedly more resistant than that of the normal controls, the carrier showing a resistance as great as that of the anemic individual.

6. This method has been found to be valuable in the detection of slight increases in fragility.

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# CARONAMIDE AS AN ADJUVANT TO PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS\*

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IN many cases of subacute bacterial endocarditis, the causative organisms are resistant to the antibiotic effect of penicillin given in ordinary therapeutic doses. This is due to the fact that in otherwise normal individuals, parenterally administered penicillin is rapidly eliminated from the blood stream, principally by way of the renal tubules,<sup>11</sup> so that unless given in massive doses, the blood concentrations of the drug are neither high nor sustained. For therapy to be effective, therefore, greater amounts of penicillin in the blood are required than are usually achieved. Higher plasma concentrations of penicillin may be obtained by the simultaneous administration of drugs which inhibit renal tubular excretion than are obtained when penicillin is given alone. Such inhibiting agents are benzoic acid or sodium benzoate,<sup>1,12</sup> diodrast,<sup>13</sup> para-aminohippuric acid,<sup>4</sup> and caronamide†.<sup>1,4,9,17</sup> The first two drugs are less effective than the others.<sup>4</sup> Diodrast and para-aminohippuric acid must be given by con-

tinuous intravenous infusion.<sup>2,13</sup> Since caronamide, which is given by mouth, is just as effective as the latter drugs, its use is much more practicable. Toxicologic effects of caronamide in experimental animals have been investigated by Beyer and his co-workers,<sup>3</sup> and were found to be minimal.

In the present study, caronamide was given with penicillin to patients with subacute bacterial endocarditis to determine whether the plasma penicillin concentrations could be increased sufficiently to arrest the disease when the organisms were resistant to the usual doses of penicillin alone. It was also hoped to learn whether caronamide in large doses would be well tolerated. Reports concerning the use of caronamide in such patients have been published elsewhere.<sup>7,10,21</sup>

**Method of Study.** Five patients with subacute bacterial endocarditis were the subjects for this investigation. Essential data concerning these patients are summarized in Table 1. Some information was obtained from 3 additional patients,

\* Penicillin for this study was furnished through the courtesy of Chas. Pfizer and Co., Inc. Caronamide for this study was furnished through the courtesy of Sharp and Dohme, Inc. Funds for this study were provided in part by the Heart Demonstration Section of the United States Public Health Service.

† Caronamide is the non-proprietary name for 4'-carboxy-phenylmethanesulfonanilide.

TABLE 1. ESSENTIAL DATA ON PATIENTS STUDIED

Patient	Cardiac Lesion	Duration of Illness, Months	Treatment before Admission	Infecting Organism	Sensitivity to Penicillin (U/ml)	Sensitivity to Streptomycin (U/ml)	Penicillin Rec'd		Caronamide Rec'd		Result
							Tot. Amt. Million u.	No. Days	Tot. Amt. gm.	No. Days	
M.C., 51/W/F	Mitral Insufficiency	7	Penicillin 2 courses, Streptomycin 2 courses*	Alpha-hem. Streptococcus	0.5	10,000	137	53	592	35	Arrested
P.G., 49/W/F	Mitral Insufficiency	10	Penicillin 3 courses	Alpha-hem. Streptococcus	0.05	1:10	60	75	444	37	Arrested
C.D., 20/W/F	Mitral Insufficiency	4½	None	Alpha-hem. Streptococcus	0.025	Not done	92	48	444	22	Arrested
H.S., 22/W/F	Mitral Stenosis and Insufficiency	1	None	Non-hemol. Strep. (Fecalis group)	Initial: 1.0 Final: 50.0	Initial: 100-300 Final: 1000-10000	311	108	1738	60	Died
L.L., 20/W/F	Aortic & Mitral Insufficiency	1½	None	Non-hemol. Strep. (Fecalis group)	0.8	1000 10000	41	24	144	8	Died

\* Penicillin treatment: Course 1—14,400,000 Units; Course 2—37,500,000 Units. Streptomycin treatment: Course 1—3 gm. daily for 15 days; Course 2—3 gm. daily for 8 days.

also observed during the period covered by this report, but not reported in detail. Data obtained as to penicillin concentrations without caronamide in these latter patients was included in the results below.

Crystalline penicillin "C" was used exclusively. Each dose, suspended in 2 ml. of physiological saline solution, was administered intramuscularly at 3-hour intervals. Individual doses used were 125,000 units, 250,000 units, or 500,000 units. Caronamide was given orally, simultaneously with the injection of penicillin. Individual doses varied from 1.0 to 5.0 gm. The longest single continuous course of caronamide therapy was in patient P.G., who received 1.5 gm. every 3 hours for 37 days. Another patient (H.S.) received 4.0 gm. every 3 hours for 31 consecutive days, followed by 5.0 gm. every 3 hours for 4 more days. Four patients received caronamide at 3-hour intervals for at least 22 consecutive days. Patient E.L., who received caronamide for 8 days only, died of causes probably unrelated to its administration, but pertinent information relative to its use was obtained. The total amounts of penicillin and caronamide received by each patient are recorded in Table 1.

The following studies were made during the control periods of penicillin administration alone, repeated during the period of caronamide administration, and again, when possible, after caronamide had been discontinued:

(1) At frequent intervals throughout the course of treatment, the penicillin plasma concentration (units per ml.) was

measured at 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours following administration of a dose of penicillin with or without caronamide. Dose response curves were thus measured. These concentrations were measured only after the patient had received therapy at that particular dosage for at least 18 to 24 hours. Penicillin assays were done by a modification of the serial dilution method of Rammelkamp,<sup>12</sup> using a standardized Group A strain of hemolytic streptococcus as the test organism.

(2) During the periods of caronamide administration the plasma concentration of this drug (mg. per 100 ml.) was measured by the method of Ziegler and Sprague,<sup>22</sup> from aliquots of the blood samples obtained for penicillin assay. No limitation of food or water intake during the measurement of dose response curves was made.

(3) Blood counts, urinalyses, and measurements of blood urea nitrogen, plasma creatinine, phenolsulfonephthalein excretion and urea clearance were done at frequent intervals.

**Results.** 1. *Enhancement of Plasma Concentration of Penicillin by Caronamide.* Table 2 presents the average penicillin plasma concentrations obtained at stated time intervals following the intramuscular administration of varying amounts of penicillin. Table 3 furnishes data obtained in similar fashion during periods of caronamide therapy. Comparison of the results in Table 2 with those in Table 3

TABLE 2. PENICILLIN PLASMA CONCENTRATIONS WITHOUT CARONAMIDE

Initial Penicillin Dose (Units)	No. of Determinations	Penicillin Plasma Concentration (U/ml) at				
		15 mins.	30 mins.	1 hour	2 hours	3 hours
125,000	M.C. 2	—	{ 1.19 1.11	{ 2.06 1.13	{ 1.02 0.52	{ 0.26 0.17
	C.S.* (1)	—	1.10	2.50	1.10	0.70
	G.D. (1)	—	1.36	0.91	—	0.11
		average	1.34	1.80	0.98	0.31
	total 4	range	1.36-1.19	0.91-2.50	0.52-1.10	0.11-0.70
250,000	11	average	—	3.0	2.27	0.67
		range	—	0.93-5.20	0.85-5.30	0.13-1.70
	—	average	12.05	11.13	6.63	4.01
500,000	4	average	12.05	11.13	6.63	4.01
		range	5.2-20.53	3.9-16.51	3.9-10.8	0.33-2.71

\* All N.S.s are given as 100 mg. per 100 ml.

reveals that the administration of caronamide resulted in significant increase in the concentration of circulating penicillin. This increase was noted in all specimens obtained during measurement of the dose response curves, and was especially apparent in the 2 hour and 3 hour specimens, where the enhancement was 3 to 10 times.

2. *Caronamide Plasma Concentrations.* Results presented in Table 4 show that the plasma concentration of caronamide varied with the dose administered, and that 3.0 or 4.0 gm. was

necessary to produce levels above 20 mg. per 100 ml. Table 5 presents data which show that when the caronamide level was above 20 mg. per 100 ml., the penicillin plasma concentrations were higher than those in specimens in which the caronamide concentration was below 20 mg. per 100 ml. This correlation between penicillin and caronamide concentrations was not demonstrated in the 15 minute specimens, but appeared to be positive in 3 hour samples. The enhancement of the penicillin concentrations when the

TABLE 3. PENICILLIN PLASMA CONCENTRATIONS WITH VARYING DOSAGE OF CARONAMIDE (1 5-4 GM. PER DOSE)

Individual Penicillin Dosage (Units)	No. of Determinations	Penicillin Plasma Concentration (U/ml) at				
		15 mins.	30 mins.	1 hour	2 hours	3 hours
125,000	M.C. (2)	—	{ 8 23 14 77	{ 10 86 (2.12	{ 7.89 8 29	{ 2 45 5 42
	P.G.* (1)	—	{ 10 5 11.16	{ — 16.49	{ 5.2 7 12	{ 2 6 3 65
	Total: 3	average range	8 23-14 77	10.86-22 12	5 2-8 29	2 6-5 53
						2 45-5 42
250,000	9	average	8 5	5.25	5 1	1 8
		range	5 2-11 1	1 8-7 3	1 4-8 9	0 9-3 7
500,000	8	average	25 52	23 85	18 01	15 09
		range	10 3-62 6	10 5-43 86	7 86-43 51	2 6-32 6
						1 14-31 35

\* This patient was 9 years old and weighed 51 lbs.

TABLE 4. CARONAMIDE CONCENTRATIONS

Dose of Caronamide (Grams)	No. of Specimens	Average Caronamide Plasma Concentration (mg./100ml.)	
		30 Minute Specimen	3 Hour Specimen
1.5 (every 3 hours)	7	15 8 Range: 3 5-38.7	11 7 Range: 1 3-29 9
3.0 (every 3 hours)	6	33.5 Range: 19 0-51 0	32 3 Range: 17 5-55 0
4.0 (every 3 hours)	3	32 1 Range: 13.5-48 9	44.7 Range: 31 1-59 4

TABLE 5. CORRELATION BETWEEN PENICILLIN AND CARONAMIDE CONCENTRATIONS

Penicillin Dose (Units)	Penicillin Conc. in 15 Min. Specimens			Penicillin Conc. in 3 Hour Specimens		
	With No Caronamide	After Caronamide		With No Caronamide	After Caronamide	
		Caron. Conc. <20 mg./100 ml	Caron. Conc. >20 mg./100 ml		Caron. Conc. <20 mg./100 ml	Caron. Conc. >20 mg./100 ml
125,000	3 4 U/ml	—	—	0 31 U/ml.	0 4 U/ml	1 97 U/ml
250,000	3 0 U/ml*	4 8 U/ml	6 2 U/ml	0 20 U/ml	0 43 U/ml	2 45 U/ml
500,000	12 04 U/ml	20 7 U/ml	23 9 U/ml	1 91 U/ml	8 5 U/ml	10 4 U/ml

\* Plasma penicillin concentration in 30 minute specimens (average).

caronamide level was greater than 20 mg. per 100 ml. was especially noticeable when the penicillin concentrations under those circumstances were compared with the concentrations reached when no caronamide was given. Table 5 shows the concentrations of penicillin obtained without caronamide for comparison with the concentrations obtained during caronamide therapy.

3. *Toxic Effects of Caronamide.* a. *Gastro-intestinal.* Among the patients reported, mild anorexia was occasionally noted during the first few days of caronamide therapy, but did not interfere with continuation of treatment. In one patient (H.S.), 4.0 gm. every third hour was well tolerated, but 5.0 gm. caused anorexia and some nausea. In two other patients, nausea and vomiting appeared promptly after institution of caronamide therapy; these symptoms precluded further use of the drug. No effects on bowel function were noted.

b. *Renal.* Abnormalities of renal excretory function were noted. With the possible exception of patient E.L., who will be considered separately, these were not of serious consequence, and all disappeared within a few days after caronamide was withdrawn. Among these other patients, none demonstrated retention of creatinine. Two patients showed a slight rise in blood urea nitrogen (each to 19 mg. per 100 ml.); one (M.C.) showed on one occasion an impairment of urica clearance to 28% of average normal function from a control value of 70%. No changes in the blood sugar, blood uric acid or carbon dioxide combining power were noted. PSP clearance was regularly reduced during periods of effective caronamide therapy. Slight to moderate albuminuria was reported often. This finding will be discussed further below. An increase of urine leukocytes was observed in three pa-

tients; in two of these, the appearance of the urine suggested gross pyuria, and in one, slight dysuria was noted. Each of these patients had been catheterized repeatedly, so that a cystitis might have been present.

c. *Hematologic.* No evidence of any disturbance of red or white blood corpuscles or platelets was observed during caronamide administration, regardless of dosage employed or duration of therapy.

d. *Dermatologic.* In only one patient (M.C.), a morbilliform rash appeared. This had the characteristics of a penicillin dermatitis, and disappeared when the type of penicillin was changed despite the fact that caronamide was continued. No other skin manifestations were observed.

4. *Clinical Results and Post-mortem Findings.* Of the 5 patients in this report, 3 were thought to be arrested after a minimum follow-up period of 10 months. One of the 3 (M.C.), had previously failed to respond to repeated courses of penicillin and streptomycin in dosage adequate for most patients (Table 1). Patients P.G. and G.D. were desperately ill at the time of admission and throughout much of their hospital stay. Each suffered major cerebral emboli which produced complete hemiplegia. Patient G.D. recovered completely, but patient P.G. still has evidence of cerebral damage.

Necropsies were done on the 2 remaining patients. Patient H.S., infected with a highly resistant strain of non-hemolytic streptococcus, received large doses of both penicillin and caronamide for prolonged periods. Although high plasma concentrations of penicillin were obtained, therapy obviously was inadequate. Terminally, a 20-day course of bacitracin was likewise ineffective. This patient became pregnant between courses of treatment, and received caronamide during the

first 10 weeks of pregnancy. Three months after the last dose of caronamide, in the 22nd week of pregnancy, the patient spontaneously aborted a well-developed male fetus. Necropsy examination of the fetus showed only evidence of prematurity. Findings at necropsy in the patient herself were limited to those which ordinarily accompany fatal subacute bacterial endocarditis. No lesions of the kidneys attributable to the prolonged caronamide therapy were observed. Patient E.L., likewise infected with a penicillin-resistant organism, received caronamide for 4 days. On the second day of treatment, she was given a blood transfusion. After 100 ml. of blood had been received, she developed a chill and subsequent fever. Because a transfusion reaction was suggested by these signs, the transfusion was discontinued. Unfortunately, the donor blood was not rechecked with the patient's serum for agglutination. On the fourth day of caronamide therapy, she developed marked oliguria, elevation of the BUN from the pre-treatment level of 9 mg. per 100 ml. to 28 mg., and signs of rapidly increasing congestive heart failure. Albuminuria and the appearance of many red and white corpuscles in the urine were observed for the first time. (An earlier urinalysis done 6 days before showed a few red cells per high power field.) Since caronamide was suspected of having precipitated oliguria the drug was withdrawn, and treatment for congestive failure was instituted. She improved somewhat, and caronamide was restarted one week later on a smaller dosage schedule. However, 10 days after the initial appearance of oliguria, she suffered a massive basilar subarachnoid hemorrhage and died. During the pre-caronamide period, this patient showed penicillin levels after an injection of 250,000 units as follows:

2.8 U per ml. of plasma in the 30 minute and 1 hour specimens and less than 0.06 U/ml. in the 3-hour specimen. On the day oliguria developed, her concentrations after a similar dose were 8.9 U/ml. in the 1-hour specimen and 1.4 U/ml. in the 2-hour specimen. Caronamide concentrations were not measured at this time. At necropsy, in addition to the lesions anticipated in a case of subacute bacterial endocarditis, there was an acute diffuse glomerulonephritis. None of the glomeruli were normal, and only rarely did a capillary loop contain erythrocytes. The endothelial cells of the capillary loops were generally swollen, and the lumens were obliterated. There were many fibrinous adhesions between tufts and capsules. In a few glomeruli, the epithelium of the tufts was proliferating. Nearly all of the proximal and distal convoluted tubules were degenerating, and many of the epithelial cells were necrotic. Many of the nephrons also were distended with erythrocytes. Some of these were freshly extravasated, others were laked. There were occasional casts of hemoglobin, but in most, fragments of erythrocytes were visible. Hyalin casts were also present.

**Discussion.** Caronamide has been shown by several investigations to enhance penicillin plasma concentrations.<sup>9,16,19</sup> We have been able to confirm these observations. Despite the fact that many dose response curves during caronamide administration were taken following doses of the drug which are presumed to be inadequate, as will be discussed below, the highest penicillin concentrations during the control period were, in general, not as high as the lowest concentrations obtained with caronamide. Similarly, the maximum levels reached during adequate caronamide therapy exceed the maximum levels found when carona-

mide dosage was inadequate or withheld. These differences were most striking in the 2-hour and 3-hour samples.

In reviewing the data in Tables 2 and 3, it is noted that in both tables, which give penicillin concentrations with and without caronamide, the concentrations following 125,000 units were higher than after 250,000 units were administered. This discrepancy was unexpected, since one may assume that penicillin plasma concentrations will vary directly with the dose employed. It appears to be the result of several factors. First, 2 of the 4 dose response curves measured with 125,000 units of penicillin were done in patient M.C., who at 51 years of age was much older than the other patients. A third curve in this group was done in a patient admitted with considerable impairment of renal function, as evidenced by a BUN concentration of 40 mg. per 100 ml. on admission. Similarly, 2 of the 3 curves measured with 125,000 units plus caronamide were done in patient M.C. Increased age and clinically impaired renal function might be expected to yield higher penicillin concentrations in the plasma than would be found in the absence of these conditions. Thus the average values may have been elevated. Secondly, the 125,000 unit curves on patient M.C. were assayed at another laboratory. The penicillin employed by this laboratory in the assays and that given to the patient were at first obtained from different manufacturers. As this study continued, all later assays were done in the William Pepper Laboratory. In the latter, penicillin concentrations were lower than those found in the former laboratory when duplicate specimens were examined in each. However, when both laboratories used penicillin from the same source for the standard in carrying

out the tests, results were generally the same. Thus, the higher levels obtained with 125,000 units may reflect differences in laboratory technique, which were later corrected. Nevertheless, administration of caronamide in each instance resulted in enhancement of penicillin concentrations.

In the treatment of subacute bacterial endocarditis, high concentrations of penicillin are desirable and often necessary. In several recent reports,<sup>11, 15, 20</sup> extremely large doses of penicillin were required in some instances to control the infection. Whatever concentration of penicillin is thought to be necessary, and whether a high plateau of concentration or intermittent high peaks of concentration are regarded as more effective, it is apparent that attainment of these aims is facilitated when caronamide is employed as an adjuvant. Results similar to those reported in this study have been published, in which patients with subacute bacterial endocarditis were treated with penicillin and caronamide.<sup>7, 10, 21</sup>

When caronamide concentrations exceeded 20 mg. per 100 ml. the effect of the drug on penicillin concentration was consistent. At lower caronamide concentrations, the effect was more variable and less striking. Three gm. of caronamide every third hour usually maintained caronamide blood levels in the effective range, and this dose is therefore recommended for therapeutic purposes. This finding is in agreement with results published elsewhere.<sup>2</sup> In addition, caronamide was used for periods up to 60 days in these patients, and such prolongation of therapy appeared to be feasible.

Nausea and vomiting were at times sufficiently severe to preclude further administration of the drug. Otherwise, no important toxic effects were observed, except possibly in patient E.L. The acute glomerulonephritis demon-

strated at necropsy in that case was not recognized clinically. The higher than average plasma penicillin concentrations might well be due to renal insufficiency. Whether the transfusion reaction aggravated the lesion is uncertain. Furthermore, it cannot be determined whether the administration of caronamide had a deleterious effect on already damaged nephrons. It is unlikely however that either or both of these factors were primarily responsible for the renal lesion, since the appearance of erythrocytes in the urine antedated the transfusion and the administration of caronamide.

Transient urinary abnormalities and mild disturbances of renal excretory functions were noted in the other patients, but disappeared promptly when caronamide was discontinued. Albuminuria was reported frequently, based on the results of the heat and acid test. Since completing this study we have found that in the urine of patients being treated with caronamide, the precipitate formed on the addition of acid may be composed entirely of caronamide itself. If the acid is added before heating, and the precipitate separated by centrifugation, the supernatant urine will usually remain clear upon heating. Caronamide precipitation may have been responsible for some of the tests reported positive for proteinuria in these patients. On the other hand, some of the urinary abnormalities found in these patients may have been produced by the focal embolic glomerulonephritis often found in patients with subacute bacterial endocarditis.

In patient M.C., augmentation of penicillin plasma concentration by caronamide was followed by arrest of infection, although the infection had not been arrested previously by several courses of penicillin or streptomycin alone. Although patients P.G. and

G.D. were infected with penicillin-sensitive organisms, because of the severity of their disease, caronamide and penicillin were used in large doses, and it is believed that the ultimate enhancement of penicillin plasma levels by caronamide contributed materially to their recovery.

Patient H.S. represents a therapeutic failure of the regimen employed. It is obvious that she never attained plasma concentrations of penicillin of sufficient magnitude to overcome an organism which developed high resistance. Whether enormous doses of penicillin, such as 20,000,000 units daily or even higher, would have resulted in recovery is not known. In this patient, the use of caronamide during pregnancy probably had no effect on the development of the fetus. We do not believe that the drug was in any way responsible for the abortion, since the miscarriage occurred three months after the last dose of caronamide was administered.

In conclusion we believe that caronamide has value as an adjuvant to penicillin in the treatment of subacute bacterial endocarditis, especially in those patients in whom elevation of penicillin plasma concentrations for prolonged periods is considered advisable. In the limited experience to date, serious hazards in its use have not been demonstrated. Its routine use in mild infections with penicillin-sensitive organisms does not appear warranted at the present time. The apparently low toxicity and ease of administration are desirable characteristics of the drug.

**Summary.** 1. Patients with subacute bacterial endocarditis were treated with large doses of penicillin and caronamide. Caronamide was used in some patients for periods up to 60 days without apparent harmful effect.



Enhancement of penicillin plasma concentrations was noted uniformly.

2. Mild effects on renal function were observed during periods of caronamide therapy. Except for one patient with major renal involvement, these effects were of no serious consequence and disappeared after withdrawal of the drug. False positives for proteinuria were frequently obtained because caronamide was precipitated in an acid medium. Whether in one patient caronamide played an etiologic role in the major renal disturbance which occurred is uncertain.

3. Three gm. of caronamide given orally every 3 hours resulted in therapeutically adequate plasma concentrations of caronamide.

4. Nausea and vomiting following administration of caronamide may preclude its further use in some patients.

5. The use of caronamide as an adjuvant to penicillin in the therapeutic management of subacute bacterial endocarditis is suggested. It can as a rule be continued throughout the entire period of penicillin therapy without toxic effects.

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## FUNCTIONAL SYSTOLIC MURMURS IN CHILDREN

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IN describing cardiac murmurs, the terms "functional" and "organic" are often employed though their use is not always clear. For instance, murmurs heard in individuals with anemia or with thyrotoxicosis are often labeled "functional." What is actually meant is that the murmurs are not caused by structural or organic changes in the heart and that the cure of the underlying disease will result in their disappearance. On the other hand, the term "organic" has been restricted to cases where it is believed that valvular changes are present, emphasizing thereby that murmurs due to ventricular dilatation should be termed "functional." If one could differentiate in every case between ventricular dilatation and valvular disease such an implication would not be objectionable. However, at times it may be difficult to determine whether a deformed valve or a dilated heart with a normal valve is responsible for the murmur. In such cases the terms "functional" and "organic" are clearly confusing.

To avoid such confusion it is preferable to apply the term "functional murmur" only to individuals in whom structural valvular changes can be reasonably excluded and who are free of any disease, general or cardiac, that is known to cause a systolic murmur. These criteria formed the basis for the selection of the children used in this study since, as far as could be discovered, the only abnormality present was the systolic murmur. For such children the term "functional" has the advantage of an established meaning and, even if vague, has the merit of wide usage.

Recent studies have shown that from 8 to 20%<sup>13,14,16</sup> of school children present systolic murmurs that are thought to be functional. Perhaps because of a different interpretation of "functional", these figures are far below those earlier published, where it was stated that functional systolic murmurs were found in from 66 to 71% of the children examined.<sup>6</sup> However, even 8 to 20% represent a large number of children whose cardiovascular system must be studied in order to rule out organic disease. This may at times be very difficult since the differentiation between organic and functional murmurs can tax the diagnostic ingenuity of the most skilled physician. Thus, for example, about 25% of all children examined by the Cardiac Consultation Service<sup>2</sup> are classified as possible heart disease, most commonly on the basis of a systolic murmur whose significance could not be definitely evaluated. Similar difficulties were encountered in adults by Levy and his co-workers,<sup>9</sup> who found that the significance of late systolic murmurs was one of the moot points of diagnosis.

The foregoing considerations indicate that the recognition and the significance of functional systolic murmurs deserve further study. It was therefore deemed of interest to analyze in detail the functional systolic murmurs heard in 300 children. The results of this analysis as well as a discussion of the problem of the physical activity in these children form the basis of the communication.

Material. The 300 children observed in this study were referred to the Cardiac Consultation Service either by school or by private

physicians. In all, the sole cardiac abnormality was a systolic murmur. All the children were between 6 and 14 years of age. A careful history, a physical and a fluoroscopic examination with particular emphasis on past or present evidence of rheumatic fever or of cardiovascular disease were obtained on each child. Whenever indicated, laboratory examinations were done to rule out the presence of infection, especially rheumatic fever. Those who gave a history of definite or possible rheumatic fever, or who showed any physical, fluoroscopic or electrocardiographic deviation from normal standards were excluded from the present study. After an appraisal of all the data thus obtained, the systolic murmurs of the 300 children were classified as "functional." This diagnosis when made by a well-trained cardiologist on the basis of a careful history and complete cardiovascular examination has been found to be correct in almost 98% of the cases.<sup>11,15</sup> Hence, the murmurs analyzed in this report can be accepted as characteristic of the functional type as defined above.

In describing murmurs heard in children examined in the Cardiac Consultation Service, the cardiologists employed a standard form and nomenclature. The time, site of maximum intensity, quality, duration and transmission of the murmurs as well as the effects of position and exercise on them were described.

#### Description of Functional Murmurs.

1. *Time in cycle.* All of the murmurs were systolic in time. In the literature practically every discussion of functional murmurs makes a point of stating that such murmurs are *almost* invariably systolic in time, thus suggesting that on rare occasions they may be heard during diastole. The latter have been heard in children and in adults with severe anemia and are ascribed to cardiac dilatation.<sup>4,12</sup> Hence, they have not been included in this study. Moreover, such diastolic murmurs have never been described in non-anemic individuals. It is well to stress this point, for a faint high pitched blowing diastolic murmur along the left border of the sternum characteristic of aortic insufficiency, may be the only manifestation of rheumatic heart disease. When in such a case a history of rheumatic fever is absent and cardiac en-

largement is not demonstrable, the question may be raised whether the diastolic murmur is functional in character. Under such circumstances it is important to recognize that in the absence of a severe degree of anemia, a diastolic murmur is due to organic disease of the heart.

2. *Site of Maximum Intensity.* It may be seen (Table 1) that the murmurs were heard at various sites along the left border of the sternum as well as at the apex. In the present series, 69% of the murmurs were located in the left 2d or 3d space and 31% were located at or near the apical region. When the murmur is best heard at the apex (17% in this series) it may cause considerable confusion, particularly if the murmur is moderately long and loud and is transmitted for a short distance to the left. Murmurs of this type may require careful and repeated observations before a final decision can be made. When in the course of time such murmurs become inaudible one assumes that they were not due to structural changes in the valve. However, the murmur of mitral insufficiency may, too, become inaudible after a time.<sup>2</sup> Wilson's observations<sup>17</sup> indicate that these murmurs are by no means constant and that in 8% of her cases they could not be heard on some examinations. Moreover, "The murmur (of acquired organic heart disease) was indistinguishable from the so-called benign systolic murmurs in the majority of children at some time during the period of observation." One can therefore only conjecture whether some of the apical systolic murmurs heard in the present series of cases were not due to mitral insufficiency. In the absence of a history of rheumatic infection and in the absence of evidence of cardiac enlargement it certainly was not justifiable to assume the presence of organic heart disease in these cases.

Murmurs best heard at or near the

pulmonic area do not present such difficulties and are more characteristic of functional murmurs. Nevertheless even faint and short murmurs heard at this site cannot be dismissed as unimportant without a fluoroscopic examination since, now and then, fluoroscopic examination of the chest will reveal an abnormal cardiovascular silhouette highly suggestive of a congenital heart defect. It appears, therefore, that the site of maximum intensity cannot be used as an absolute criterion to distinguish between an organic and a functional murmur.

3. *Quality*. Various terms have been used to describe the character of murmurs, both organic and functional. No one term is applicable in all instances since the quality of murmurs varies considerably and the ability of the indi-

vidual to classify auditory impressions is equally varied. The terms rough, blowing, musical and blowing-musical were used to describe the acoustic impressions of the physicians examining the children of this study. It may be seen (Table 1) that only 3% were classified as rough, 36% were characterized as blowing and 55% as musical. A small number, 6%, appeared to have both musical and blowing qualities. In a few instances it was noted that the murmurs which had a musical character when the child was at rest assumed a blowing quality when the heart accelerated after exercise.

More than 50% of the murmurs were accordingly musical in character. At times murmurs of this type could be better described as having a buzzing quality, a characteristic which appears

✓ TABLE 1.—ANALYSIS OF DATA ON 300 FUNCTIONAL MURMURS

		Number	Per cent
Site of Maximum Intensity.	1. Pulmonic Area	65	22
	2. Left 3rd Space	143	47
	3. Left 4th Space	42	14
	4. Apex	50	17
Quality.	1. Rough	15	3
	2. Blowing	108	36
	3. Musical	164	55
	4. Blowing-musical	13	6
Intensity.	1. Faint	200	66.6
	2. Moderate	100	33.3
Transmission.	1. From left 2nd Space—65 cases		
	Localized	24	37
	Down left sternal border	41	63
	2. From left 3rd Space—143 cases		
	Localized	23	16
	Up and down left sternal border	52	36
	Up left sternal border	22	15
	Down left shoulder border	46	33
	3. From left 4th Space—42 cases		
	Localized	5	12
	Up left sternal border	35	83
	Short distance to left	2	5
	4. From Apex—50 cases		
Effect of Change in Position.	Localized	8	15
	Up left sternal border	35	70
	Short distance to left	7	15
	1. No change	33	11
	2. Louder in recumbency	184	61
	3. Louder in standing position	40	13
	4. Heard only in recumbency	20	7
	5. Heard only in standing position	5	1.5
	6. Heard only in recumbency after exercise	15	4.5
	7. Heard only in standing position after exercise	3	1
Effect of Exercise.	1. No change	32	11
	2. Louder	160	53
	3. Fainter	50	17
	4. Absent	23	7
	5. Murmurs appeared only after exercise	35	12

to be confined to functional murmurs. It is of interest to note that in a previous study<sup>1</sup> in which sound tracings were used in an attempt to distinguish organic from functional murmurs, a similar finding was observed. Organic murmurs do not appear to possess this peculiar buzzing character, a fact which may be used to advantage in the differential diagnosis.

4. *Duration.* In 274 cases the murmurs were short, while in the remaining instances they were moderately long. No instance of a prolonged murmur was encountered in this series. Because the time interval during which the functional murmurs are audible is frequently so short it may be difficult to decide whether an actual murmur is present or whether the adventitious sound is merely an impure first heart sound. In this series there were 33 children who were referred to the Cardiac Consultation Service with a diagnosis of possible heart disease because the referring physician had heard or believed he had heard a systolic murmur but in whom the cardiologist could not detect a murmur in any position even after exercise. This difference in findings may have been due to confusion between a loud and impure first sound and a short faint systolic murmur. Levine's advice may well be heeded: "By definition a systolic murmur, no matter how faint, must have duration; it must last an appreciable interval into systole between the first and second heart sound."<sup>7</sup>

5. *Intensity.* In this study the intensity of the murmurs was described in terms of faint, moderate or loud. No instance of a loud functional murmur was found. Faint murmurs were heard in 20 (6%) of the children, and murmurs of moderate intensity in the remaining 100 cases. Using Levine's<sup>7</sup> method of grading the intensity of murmurs, one could say that the faint murmurs belonged to grades 1 and 2,

whereas those of moderate intensity corresponded to grade 3. Levine<sup>3</sup> concluded from a study of 1000 non-cardiac individuals, *all adults*, that systolic murmurs of grade 1 were fairly common, those of grade 2 less frequent and those of grade 3, quite rare. In contrast, 1/3 of the systolic murmurs of this series were sufficiently loud to be termed grade 3 intensity. These differences can probably be ascribed to the greater area of relative cardiac dullness during childhood and to the thinner chest wall, both factors permitting murmurs to be heard more easily.

6. *Transmission.* As will be seen in Table 1, the murmurs were localized in 60 cases. In the remaining, some degree of transmission was present regardless of the site of maximum audibility. Apical systolic murmurs were of particular interest in this regard, since, as already said murmurs in this region give rise to the major difficulties in diagnosis. Only 15% of the apical murmurs were localized, whereas 70% were transmitted to and up along the left sternal border and 15% were transmitted for some distance to the left of the apex. Equally variable was the transmission of the murmurs heard at the other sites: 16% of those heard at the left 3d interspace and 37% of those heard at the left 2d interspace were localized; the remainder were transmitted up or down the left sternal border. Wide transmission of murmurs was not encountered in this series, probably because none of the murmurs were very loud. Thus, in no instance was an apical murmur transmitted to the axilla or a para-sternal murmur transmitted all over the pre-cordial area. While the absence of wide transmission is regarded as a distinctive feature of functional murmurs it is equally well recognized that the murmur of mitral insufficiency may also be faint and transmitted to only a limited extent.

Since it is generally accepted that

the extent of transmission of a murmur is dependent mainly on its intensity, an attempt was made to determine this correlation in the present series. As may be seen from Table 2, only 20% of the non-transmitted murmurs were of moderate intensity; the rest were faint. On the other hand, 63% of the murmurs that were transmitted were also faint. These findings suggest that

TABLE 2.—RELATION OF TRANSMISSION TO INTENSITY OF MURMUR

Transmission of Murmurs	Faint	Moderately loud
Localized—60 cases	48	12
Transmitted—240 cases	152	88

there may be other factors aside from the important one of intensity which determine the transmission of a functional murmur. In a previous study on functional murmurs in children it was found that these murmurs consisted mainly of high frequency vibrations.<sup>1</sup> While living tissues are generally not good conductors of sound, they may conduct high pitched vibrations more readily than the low pitched vibrations present in organic murmurs. Hence, even though the intensity of a functional murmur is faint it would be transmitted better and be more audible for a distance from its site of maximum intensity than an equally faint organic murmur. However, regardless of the factors that permit a faint functional murmur to be transmitted, the important point is that the presence of transmission of the murmur is not necessarily proof of its organic etiology.

7. *Effect of Change in Position.* Both the intensity and audibility of functional murmurs are influenced by the position of the subject. This feature has been often stressed as being of diagnostic value. "The most distinctive feature", it is stated in one discussion,<sup>5</sup> "for their (functional murmurs) identification is the change in intensity which they undergo when the subject is asked to change position. Usually best heard

in the recumbent position, they disappear, or at least are greatly diminished in intensity when the sitting or standing position is assumed." The effect of position on the murmurs analyzed in this study is summarized in Table 1. The majority (61%) of functional murmurs were loudest in recumbency and became fainter when the standing position was assumed. Only 13% were better heard in the standing position. In 11% the change from recumbent to the standing position caused no change in the intensity of the murmurs. A practically similar number could be heard only in recumbency but in some of this group the murmurs became audible only after exercise. It appears, therefore, that while there is some variability in the effect of position on the loudness of a functional murmur, one may say that, in general, the murmur diminishes in intensity when the child assumes the erect position. This feature by itself is not characteristic of functional murmurs alone for the murmur of early mitral insufficiency may react in a similar fashion and be best heard in the recumbent position.

8. *Effect of Exercise.* Functional murmurs do not respond in a uniform manner to exercise with its attendant physiological effects on the cardiovascular system. The data in Table 1 show this lack of uniformity or distinctiveness. More than half (53%) were louder after effort; 17% became fainter after exercise; 11% showed no change. Only 7% disappeared after exercise. On the other hand, in 12% of the children the murmurs appeared only after effort. The latter finding has been commented on by other observers such as Levine who noted faint systolic murmurs in normal individuals after exertion.<sup>7</sup>

Comment. The foregoing analysis of functional murmurs illustrates the well-known difficulties encountered in their recognition. They do not possess a pathognomonic feature that can dis-

tinguish them from organic murmurs. Upon what criteria, then, can one rely to designate a murmur as functional or organic? It has been stated that the various characteristics enumerated are common to both types of murmurs. Thus, in both some transmission of murmurs is found; in neither can the effect of position or of exercise on the presence or intensity of the murmur be used as conclusive evidence to sway the final appraisal. Moreover while organic murmurs are characteristically loud and long, some of them may be faint and short. On the other hand, the present study shows that functional murmurs are either faint or of moderate intensity (grades 1 to 3) and that in 92% they are of short duration. However, in individual cases, these features may fail the examining physician and a complete cardiovascular study is therefore necessary properly to evaluate the systolic murmur. The physician cannot rely on the stethoscope alone but must examine the whole child carefully with the usual technical aids "to elicit by every known means, evidence for and against the presence of cardiac disease".<sup>5</sup> The collective data thus obtained, rather than any one characteristic or finding, must be used to decide the nature of the murmur. Only by this means can one establish a correct diagnosis of a functional murmur in a high percentage of cases. The significance of an equivocal systolic murmur resides in the fact that it calls for a complete examination.

Great care is needed in the interpretation of the clinical findings, for unless the history, physical findings and roentgenologic studies are expertly correlated they too may prove to be a source of confusion. Thus, for example, there is one normal syndrome not infrequently encountered in children which may give rise to much trouble.<sup>7</sup> This syndrome consists of a triad: 1) a soft systolic murmur at the apex or pul-

monic area or both; 2) a loud third heart sound which produces a gallop rhythm when the heart rate is rapid; and 3) a prominent pulmonary conus with straightening of the left border of the heart as seen on fluoroscopy. Unless the examiner is on guard, he is likely to mistake this triad for rheumatic mitral valvulitis, particularly if the child also has a history of rheumatic fever. In such cases, the absence of a loud snapping first heart sound at the apex and the lack of roentgenologic evidence of cardiac enlargement, especially of left auricular enlargement, are valuable evidence against an organic basis for the clinical findings.

The physician's responsibility does not end when he has established the functional character of the murmur, for almost invariably he will be questioned as to the need for limiting the child's physical activities. Considerable confusion is apparent in this regard. In the Cardiac Consultation Service reports are frequently received from physicians recommending restrictions of the physical training program or modifications of the classroom routine at the very time that the murmur is termed functional. It is clear that the uncertainty as to the nature of functional murmurs leads some physicians to regard them with distrust despite the large amount of data indicating the absence of heart disease in such cases. It is well to emphasize once again that functional murmurs are not the result of organic disease of the heart, and moreover, as defined in this communication, are not associated with any disease process in the body. To limit physical activities under such circumstances does not appear rational. When questioned as to the desirability of these restrictions, many physicians will reply that they merely wish to "protect the child". One may well ask "protect against what? Heart failure? Rheumatic Fever?"

Whether ordinary or even moder-

ately severe physical exertion can affect adversely a child with organic heart disease of minimum to moderate extent who is free of any infection is still a moot question. None, however, will argue that the child with an isolated murmur is in any way handicapped by this murmur or that such a child needs protection from the supposed ill effects of physical activities. Since children with functional murmurs have normal cardiovascular systems, both anatomically and physiologically, it is clearly not necessary to limit their exertions because of the murmur alone. Any attempt or suggestion to do so only leads to a suspicion on the part of the child and the parent that the physician is withholding information from them and that the child is actually in a serious condition. The harm that is done to the child's development, the unnecessary mental disturbance to the parents and the danger of initiating or perpetuating a cardiac neurosis are the real dangers of such excessive protection on the part of the physician.

It is apparent in dealing with situations of this type that confusion still exists as to the significance of cardiac murmurs in children, and of the rela-

tion of normal childhood activities to heart disease and to heart failure. MacKenzie's<sup>10</sup> warning seems to have been forgotten. "Murmurs and irregularities", he stated in 1914, "have, therefore, come to occupy a place in the symptomatology which is not in accordance with their true significance."<sup>10</sup>

Summary. 1. The various features of functional murmurs\* heard in 300 school children have been analyzed. These features include the site of maximum intensity, quality, intensity, duration and effects of change of position, and of exercise on the audibility of the murmurs.

2. It is emphasized that there does not appear to be any pathognomonic feature that can distinguish a functional from an organic murmur. The only valid means of differentiating the two is to examine each child thoroughly and carefully. This has been shown to lead to correct evaluation of the systolic murmurs in the majority of cases.

3. The lack of the pathological significance of functional murmurs in otherwise normal children and the harm of restricting physical activities in such cases is discussed.

\* It will be noted that the author's use of the term "functional murmur" is restricted to those cases thought to be free of any disease, general or cardiac, that may cause systolic murmurs, thus excluding hemic murmurs, and others of non-cardiac origin. Until a satisfactory antonym can be found, for "organic murmur" (in the sense of one due to structural change in heart muscle or valve), definition of the term whenever used is necessary in the interests of clarity.—EDITOR.

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# THE ELECTROCARDIOGRAM OF HYPERTHYROID PATIENTS WITHOUT EVIDENCE OF HEART DISEASE: THE VENTRICULAR GRADIENT

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THERE is no agreement in the literature regarding the electrocardiographic pattern in hyperthyroidism. Hoffman,<sup>11</sup> the first observer to study the T waves in this disease, found a high T wave in Lead Two in 23 patients with hyperthyroidism. Hoffman also noted an apparent relationship between the high T waves and the tachycardia. Krumbhaar<sup>12</sup> described "unusually prominent T waves" in most cases of toxic goitre. In about one half of his cases the height of the T wave was markedly and persistently diminished after operation. In hyperthyroidism Hamburger *et al.*<sup>10</sup> noted little relationship between the pulse rate and the height of the T waves, although they did observe some examples of high T waves. Following surgical treatment these waves become definitely lower in most instances. McGuire and Foulger<sup>14</sup> described "high rolling T waves" in several patients with hyperthyroidism. These authors were the first to demonstrate that these same T wave changes appeared in normal subjects who were fed thyroid extract.

In contrast to the findings noted above, Don and Langley<sup>8</sup> found no relationship between the basal metabolic rate and the P and T wave changes. Rose, Wood, and Margolies<sup>15</sup> state that "while T wave changes occur immediately after partial subtotal thyroidec-

tomy in hyperthyroidism, they are not all of the same type; their occurrence is at present unpredictable, and they follow no pattern." Low and inverted T waves in hyperthyroidism have also been described by many authors. White and Aub<sup>16</sup> state that in hyperthyroidism the T wave is often low and its height does not necessarily parallel changes in the rates of metabolism; it sometimes runs converse to it. Gordan, Soley, and Chamberlain<sup>9</sup> found abnormal tracings in 30% of their cases of hyperthyroidism, but they demonstrated no correlation between the basal metabolic rate and the normality of the electrocardiogram. These authors observed, however, that following operation the T wave abnormalities had disappeared in 14 of their 17 cases.

In undertaking the present study, it was hoped that the ventricular gradient of Wilson<sup>17</sup> would aid in elucidating this problem. The ventricular gradient is the net electrical effect, as projected on to the frontal plane, produced by differences in time-course of repolarization in different regions of the ventricles. This effect is measured from the magnitude and direction of the manifest net area of the QRST complex. The magnitude of the gradient, a scalar quantity, is represented by the symbol (G), while its direction, a vector, is

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represented by the symbol ( $\dot{G}$ ). When the QRS complex is unchanged, changes in magnitude and direction of the T wave reflect changes in the magnitude and direction of the gradient.<sup>9</sup>

One of the recent developments in electrocardiography has been an increased understanding of the effect of cardiac position on the form of the ECG. The ventricular gradient is in its essence a quantitative analysis of ECG changes as they are projected on the frontal plane of the body. By the method used, however, corrections are made for alterations in the position of the heart within the chest. In consequence, ventricular gradient analysis of successive ECGs on an individual will reveal and measure intrinsic changes in the QRST complex independent of the ECG changes resulting from alterations in cardiac position alone.

The relationship between the gradient and the QRS complex is frequently altered by physiological change in the myocardium. It has been shown that in normal hearts the magnitude of the gradient, ( $G$ ), decreases when the heart rate increases.<sup>5</sup> In evaluating our data it was necessary to take into account this observation. In order to eliminate the complications introduced by myocardial disease, no patient with definite or suggestive evidence of heart disease was included in this study.

**Method:** 1. *Hyperthyroidism.* Cases with clinical hyperthyroidism were selected from the files of the Cincinnati General Hospital. Basal metabolic rates in these ranged from +20 to +50%. All doubtful cases were excluded as well as all cases with definite or suggestive evidence of heart disease. Of 19 cases thus selected it was possible to follow up 14. Eight patients had undergone subtotal thyroidectomy 6 to 12 months previous

to the follow-up ECG; 6 patients had been on thiouracil for the same period. A total of 52 ECGs on these 18 patients were studied. From each ECG the longitudinal anatomical axis of the ventricles, ( $H$ ), was estimated by the method described by Ashman,<sup>5,13</sup> and the ventricular gradient was measured as described by Ashman and Byer.<sup>3</sup> The magnitudes of the gradient, ( $G$ ), were compared to the published standards.<sup>1,11</sup>

In order to check our technique of measurement against that of Ashman and Byer we estimated the values of the gradient in a group of 30 normal controls.

2. *Thyroid Feeding.* Because of the earlier report of McGuire and Foulger,<sup>14</sup> and in order further to augment the number of hyperthyroid individuals studied, 11 normal subjects were fed 6 grains of desiccated thyroid daily for periods of 10 to 18 days. ECGs were taken at intervals and evaluated in the same manner as those of the patients.

The ages of both patients and normal subjects fed thyroid varied from 14 to 39 years. The sexes were about evenly divided.

**Results:** 1. **THE MAGNITUDE OF THE VENTRICULAR GRADIENT.** (a) *Patients.* Our findings are given in Table I. In the first column after the patient's number is given the largest magnitude of the ventricular gradient, ( $G$ ), expressed as its percentage of the mean normal value as given by Ashman,<sup>3</sup> observed in the electrocardiograms of each patient. In the next column is given the average magnitude for all the ECGs recorded on each patient before therapy. Since the normal range in ( $G$ ) is from about 40 to 160% of its average value, it will be observed that only 3 of these averages exceeded the upper limits of the normal magnitude. The average magnitude, however, is  $130.7 \pm 5.75\%$ . This is significantly greater than the average magnitude reported by Ashman for 132 normal adults (61 men and 71 women), namely  $98.6 \pm 1.5\%$ .<sup>4</sup> It is also

much greater than in our control group of 30 individuals, whose (G) averaged  $90.5 \pm 2.41\%$ .

The change after treatment is shown in Table 1 in the third column after the patient's number. The ECGs of only 14 patients were available following treatment. Before treatment (G) in this group measured  $126.7 \pm 7.0\%$ . Following treatment the average fell to  $85.0 \pm 6.3\%$ . The percentage decrease in (G)

methods in evaluating the results in this group. The fluctuations in (G) from day to day were not unexpected, since they had previously been reported as occurring in normal untreated persons.<sup>1</sup> In 10 of the 11 cases there was an increase in (G). The percentage change was obtained from an average of the progressive tracings on each patient. This change ranged from  $-4$  to  $+58\%$ . As indicated in Figure 1 the rise was

TABLE 1.—VARIATIONS IN VENTRICULAR GRADIENT MAGNITUDE DURING THERAPY OF CLINICAL HYPERTHYROIDISM

Subject	Highest Magnitude (% of Normal)	Average Magnitude (% of Normal)	Post-therapy Magnitude (% of Normal)	Percent Fall from Average	Type of Therapy
1.	195	170	167	2	Surgery
2.	139	108	60	44	Surgery
3.	123	96	66	31	Thiouracil
4.	149	132	....	....	
5.	236	143	41	71	Surgery
6.	130	95	69	27	Thiouracil
7.	84	82	46	44	Thiouracil
8.	158	158	....	....	
9.	122	122	59	51	Surgery
10.	103	96	80	16	Thiouracil
11.	157	138	98	29	Surgery
12.	151	123	71	42	Surgery
13.	228	228	145	36	Thiouracil
14.	136	112	79	30	Surgery
15.	119	115	96	17	Surgery
16.	106	106	....	....	
17.	134	134	....	....	
18.	163	163	....	....	
19.	140	140	110	21	Thiouracil

TABLE 2.—VARIATIONS IN VENTRICULAR GRADIENT MAGNITUDE OF NORMAL SUBJECTS DURING THYROID MEDICATION (6 GRAINS DAILY).

Subject	Control	Average during Medication	Percent Increase	Six Week Control
A	98	155	58	91
B	123	153	24	104
C	74	107	44	
D	124	133	8	
E	93	146	57	93
F	170	205	21	
G	117	132	13	
H	98	129	32	
I	101	97	-4	
J	105	114	8	87
K	98	106	8	

in each case is shown in the next column in the table. As indicated in the last column there was no apparent correlation between the type of therapy and the reduction in (G) following treatment.

(b). *Normal Subjects.* Table 2 shows the effect of thyroid feeding (6 grains daily for periods of 10 to 18 days). Since only 11 subjects were used, we have not separately applied statistical

steeper than this percentage suggests. Control electrocardiograms taken 6 weeks after the discontinuance of feeding were obtained on only 4 of these subjects. These showed a return to (G) values which were the same as, or lower than, the original control values. In Figure 1 are also shown the variations in (G) observed following thyroid feeding.

For the purpose of statistical treat-

ment we have combined the averages of the two groups; namely, the patients and the normal subjects fed thyroid. The mean (G) in the combined groups is  $132.1 \pm 4.21\%$ . This mean is significantly greater than the mean in our control group of 30 patients ( $90.5 \pm 2.41\%$ ).

2. RELATIONSHIP OF HEART RATE AND GRADIENT MAGNITUDE. (a) *Patients.* When the heart rates in the patients were compared with the magnitudes of the gradients, no good correlation was found. But when all those cases were excluded in which there was abnormal deviation of the gradient, correlation shown in Figure 2 was found. In general the more rapid the heart rate, the greater percentage increase in (G).

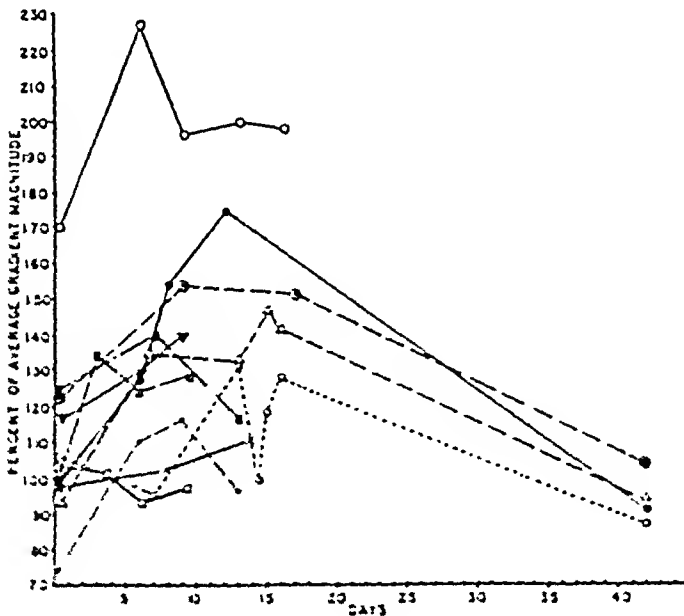
(b). *Normal Subjects.* One of our subjects who seemed normal clinically proved to have a gradient which lay outside the normal range as given by Ashman.<sup>4</sup> When this subject was excluded, as shown in Figure 3, a good

correlation was found between the heart rate and (G).

Even in the absence of rate increase, however, (G) is increased in magnitude. This demonstrates that the increase in magnitude observed after rate increase is not due to inaccuracy in the standard used for comparison.

3. DEVIATION OF ( $\hat{C}$ ), THE DIRECTION OF THE GRADIENT, FROM ITS ESTIMATED MEAN NORMAL DIRECTION. The method of estimating the average normal direction of the gradient, ( $\hat{C}$ ) has been given by Ashman.<sup>4</sup> In general, according to his findings, ( $\hat{C}$ ) should not deviate by more than  $15^\circ$  to the right or more than  $28^\circ$  to the left of its estimated average normal direction unless the manifest net area of QRS axis ( $A_{QRS}$ ) is small. In this latter case the normal range of deviation of ( $\hat{C}$ ) is somewhat greater.

We studied 52 electrocardiograms taken before therapy on 18 patients with respect to deviation of  $\hat{C}$ . The average deviation (or diversion as Bay-



ley calls it<sup>7</sup>), of  $(\hat{G})$  was  $13.5 \pm 2.2^\circ$  to the right of its estimated normal direction, but in 10 of these cases the direction of  $(\hat{G})$  was still within normal range. In 8 patients the deviation of  $(\hat{G})$  was 15 or more degrees to the right. For comparison with these hyperthyroid cases we estimated the deviation of  $(\hat{G})$  in a series of 30 patients without thyroid or cardiac disease. In this group the average direction of  $(\hat{G})$  was  $1.30 \pm 1.18^\circ$  to left of the estimated mean normal direction.

The difference in the mean  $(\hat{G})$  direction in the two groups is  $14.8 \pm 2.5^\circ$  and, therefore, significant.

Following treatment by surgery or by thiouracil not all the gradients which were deviated to the right returned to normal. In Case 1,  $(\hat{G})$  lay 15 degrees to the right both before and after treatment. In Case 13,  $(\hat{G})$  was essentially unchanged after treatment at  $19^\circ$  to the right. In Case 5, the change was from an average rightward diversion (3E CGs) of  $38^\circ$  to  $20^\circ$ . In-

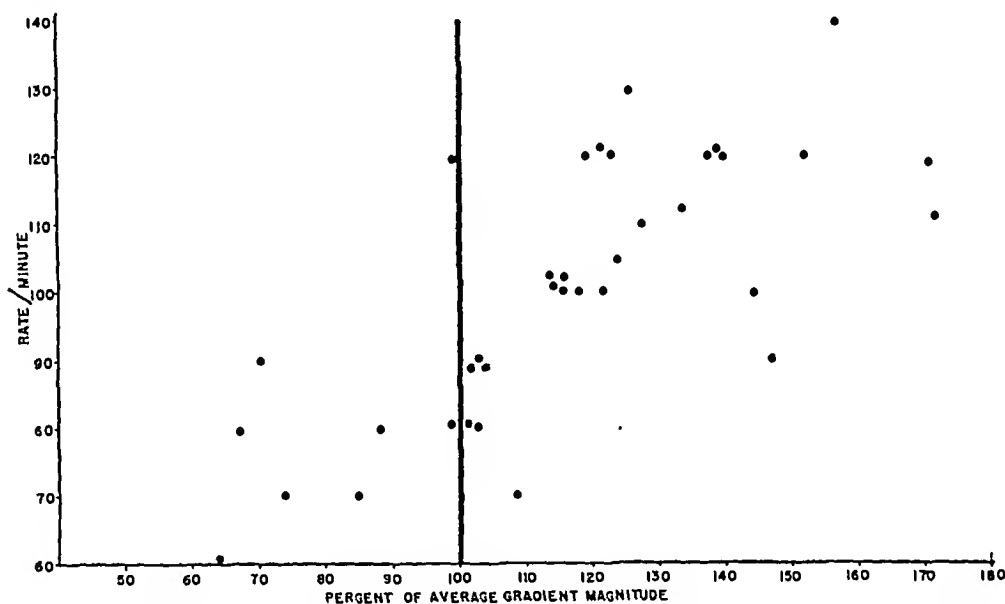


FIG. 2.—Patients with clinical hyperthyroidism having ventricular gradients showing no significant deviation from normal.

Individual readings for ventricular gradient magnitude are plotted against heart rate.

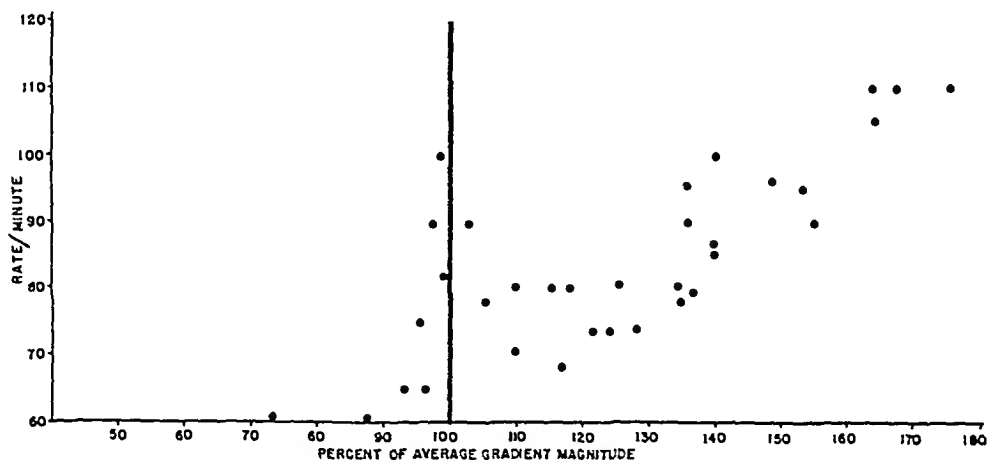


FIG. 3.—Normal subjects fed thyroid having ventricular gradients showing no significant deviation from normal.

Individual readings for ventricular gradient magnitude are plotted against heart rate.

cluding these 3 cases the mean direction of the gradient following treatment was  $1.5 \pm 2.7^\circ$  to the right in the 14 cases with follow-up ECGs. In Case 9, ( $\bar{G}$ ) was deviated  $13.5^\circ$  to the right before, and  $29^\circ$  to the left after treatment.

Among the normal subjects fed thyroid no significant changes were observed in the direction of the gradient either during the feeding period or in the subsequently recorded control ECGs.

4. No correlation was found between the percentage increase in ( $G$ ) and the duration of the Q-T interval, or between the latter and the deviation of ( $\bar{G}$ ).

5. No correlation was found to exist between the ECC changes and the basal metabolic rate in these cases.

**Discussion.** In order to make our analysis of the electrocardiograms in hyperthyroidism quantitative and meaningful it was essential to analyze the T-wave in terms of the ventricular gradient of Wilson. Now that the data have been presented, it is possible to translate our findings into ordinary electrocardiographic terminology. The increase in the gradient, observed both in the series of patients and the normal subjects fed thyroid, means that in relation to the magnitude of the QRS complex and minute heart rate, the T-waves are of greater magnitude than the average seen in normal persons. In only 3 of the patients and in 3 of the normal subjects fed thyroid, however, did the T-waves exceed the usual normal range in magnitude; yet the average size of the T-waves was definitely greater than in a comparable group of normal persons whose heart rates and S magnitudes were the same. In comparison with the T-waves of normal persons whose heart rates are not increased, the T-waves in hyperthyroidism, where the heart rate is controlled, are actually not abnormal, and in this sense we

cannot agree that unusually high T-waves are a universal finding in hyperthyroidism as some of the earlier reports suggested. We do believe, however, that in comparison with the T-waves observed in other types of tachycardia occurring at rest, the T-waves seen in hyperthyroidism are on the average increased in height.<sup>3</sup> In this regard they may be similar to the T-waves seen immediately following exercise which are often larger than normal.<sup>6</sup> Aside from the obvious suggestion that the relatively large gradient in hyperthyroidism may be related in some unknown manner to the elevated metabolic rate or the augmented cardiac output, nothing can be said regarding the cause of this increase.

The discovery that the ventricular gradient tends to become deviated to the right in hyperthyroidism is, we believe, a new finding. Translated into ordinary terminology, this means that, relative to the QRS pattern which is present,  $T_1$  is low relative to  $T_2$ . Since, in proportion to the heart rate, the T-waves in hyperthyroidism are larger than in control groups, this may best be interpreted as an increase in  $T_2$  relative to  $T_1$ ; that is, there tends to be a rightward deviation of the electrical axis of that wave. In cardiac patients this is often a sign of early but chronic myocardial ischemia or fatigue in the lateral wall of the left ventricle. Slight myocardial fatigue, related to increased cardiac work, may possibly be the factor which is responsible for this change seen in some of our hyperthyroid patients. Since it is unassociated with prolongation of the Q-T interval, there is no indication of general ischemia or fatigue affecting the whole ventricular myocardium. The fact that none of the normal subjects fed thyroid showed a similar change may be interpreted as indicating that it appears only after the increased cardiac work has persisted for a relatively long time. After

treatment the rightward deviation of the gradient disappeared in most of the patients who showed it. It has been previously noted that the Q-T interval is normal in thyrotoxicosis when the ECG is essentially normal.<sup>2</sup>

Support for the suggestion that rightward deviation of the gradient is a "fatigue" phenomenon is given by observations detailed above (paragraph 3 of the results); namely, that the relative increase in the magnitude, (G), with increase in heart rate holds only in that group of hyperthyroid individuals whose gradient directions are within normal range. La Due and Ashman<sup>13</sup> have noted a very large variation in (G) in patients with acute glomerulonephritis and abnormal ECG findings. It is, therefore, probably to be expected that when analogous ECG changes occur in hyperthyroidism, the correlation between rate and (G) should disappear.

**Summary.** In hyperthyroid patients who present no clinical manifestations of myocardial disease the ventricular gradient of Wilson, and hence the T waves, are larger than in normal persons with comparable heart rates.

In many such persons the direction of the gradient shows a diversion or

deviation toward the right. This suggests a moderate degree of myocardial "fatigue" but the Q-T interval is not prolonged as it is in many patients with T waves of the so-called ischemic type.

In normal persons who are fed desiccated thyroid, equal relative increase in gradient and T wave magnitude occur, but no signs of myocardial fatigue (deviation of the gradient) develop, even after 18 days of thyroid feeding.

In both hyperthyroid patients and in normal subjects fed thyroid there is a fair correlation between heart rate and relative increase in gradient magnitude, providing the ECG is normal, that is, reveals no deviation of the gradient. No correlation was discovered between the gradient and the basal metabolic rate.

Following treatment by operation or thiouracil in patients and after discontinuance of feeding in normal subjects, the abnormal deviation of ( $\hat{G}$ ), when present, tended to disappear and the magnitude of (G) diminished toward normal.

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# TREATMENT OF PNEUMONIA WITH INTRAMUSCULAR AQUEOUS PENICILLIN ONCE A DAY

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THE clinical use of aqueous penicillin in the treatment of bacterial infections has involved frequent injections, to the inconvenience of patient, nurse and physician. This regimen, in most cases, has made penicillin therapy a hospital procedure. The frequent dosage schemes in common use have been based on the assumption that adequate treatment depends on maintaining the blood concentration of penicillin above a certain minimal level. That level has been dictated by the sensitivity of the infecting organism to the action of penicillin *in vitro*.

Tillett and his associates<sup>1,2</sup> in 1944 demonstrated that pneumococcal pneumonia could be successfully treated with penicillin when the drug is omitted for 12 to 16 hours at night. During 1946, Jawetz<sup>3</sup> showed that the antibiotic effect of penicillin outlasts the measurable blood levels in mice infected with streptococcus. This was confirmed by Zubrod<sup>4</sup> and the importance of the blood level in penicillin therapy has been re-evaluated by Eagle<sup>5</sup> and by Marshall.<sup>6</sup> Tompsett<sup>7</sup> and his associates mention 26 cases of pneumonia successfully treated with 1000 units aqueous penicillin intramuscularly twice a day until defervescence occurred, followed by one

penicillin-G intramuscularly once a day until the temperature remains normal for 3 days.

**Method and Material.** Thirty consecutive cases of pneumonia admitted to the medical wards during the first 3 months of 1948 form the material for this report. On admission, the diagnosis of pneumonia was made on the clinical history and physical examination, and was corroborated by roentgenography. A specimen of sputum was collected from all but 2 patients and a sample of blood for culture in 24 cases. Then the patient was given an injection of 300,000 units aqueous penicillin-G intramuscularly, regardless of what time of day or night the patient was admitted. This was repeated at noon of each successive day until the temperature was normal for 3 days.

There were 15 males and 15 females ranging in age from 16 to 72 years who were admitted in the 1st to 5th day of illness (the onset of the pneumonic process was taken as occurring with the chill and pleural pain). On the basis of the clinical appearance, the roentgenogram and complications, the degree of illness was graded as severe in 5, moderate in 11, and mild in 5 cases. Blood culture showing pneumococcus was positive in 1 case, a mild one. Sputum studies were made in 25 cases and pneumococcus was found in 26, associated sometimes with various organisms, including non-hemolytic streptococcus, *Strep. viridans*, *B. fragilis*, and *S. aureus*. One lobe was involved in 25 cases, 2 lobes in 2 cases, and 3 lobes in 1 case. Another case showed a central pneumonic process and

describes the treatment of pneumonia in man with 20,000 units aqueous

in the last case, the roentgenogram showed a bronchopneumonia of both lower lobes. One daily injection was continued for 4 to 13 days, usually 5 to 7 days. Two cases received 4 injections and 5 cases received more than 7. Patients were kept in the hospital until the roentgenogram showed complete resolution or until delayed resolution was adequately studied.

**Results.** The analysis of results in the 30 cases appears in Table 1. There were 4 groups according to response to treatment. Group 1 included 18 cases (60% of the total number) in which cure was prompt and the temperature dropped to normal by crisis within 12 to 36 hours. Five cases were classified as mild, 10 moderate and 3 severe. There were 17 lobar pneumonias and 1 bronchopneumonia. Seventeen cases showed pneumococci in the sputum, associated with streptococci in 5 cases, *Staphylococcus aureus* in 2, and *B. influenzae* in 2 cases. One of the patients with lobar pneumonia had *Strep. viridans* in pure culture in her sputum.\* Treatment in this group consisted of 4 to 7 injections. The following complications occurred: 4 cases of latent syphilis, 1 pleural effusion, 1 hepatitis, 1 case of delayed resolution (roentgenographic signs still present after 4 weeks of observation), and 1 patient was operated upon on admission for a strangulated umbilical hernia. One patient developed a recurrence in another lobe on his 16th hospital day just as his first lesion showed complete resolution; the same treatment was repeated and again produced prompt cure.

Group 2 consisted of 9 cases (30% of the total) who responded to treat-

ment more slowly and whose temperature fell by lysis. Three cases were mild, 2 moderate and 4 severe. The percentage of severe cases was therefore much higher in this group than in the first group. In 8 cases the lesion was lobar and in 1 case central in location. Sputum examination was done in 8 cases and pneumococci were found in all. Streptococci were found in a higher proportion of these cases than in patients of Group 1. Mixed infection may be a factor in causing response to penicillin by lysis rather than by crisis. Since the temperature fell by lysis in this group, as many as 13 injections were required in contrast to 4 to 7 injections in the crisis group. Complications consisted of: hepatitis in 1 patient, scarlet fever in 1, latent syphilis in 1, delayed resolution in 2, and pleural effusion in 1. The patients whose resolution was delayed more than 4 weeks were both bronchoscoped but no endobronchial or tracheal lesions were found; bronchograms were done in both cases and one showed bronchiectasis. Another severely ill patient showed a possible cavity 2 cm. in diameter in the center of the consolidated lobe. She had no symptoms or signs of lung abscess and there was no history of foreign body aspiration. Her response to treatment was prompt. The cavity disappeared as the pneumonia resolved. Serial roentgenograms were taken and complete recovery was noted at the time of discharge. One patient was admitted with a pleural effusion. He was a 32 year old male, moderately ill, who had received a sulfonamide and penicillin for 4 days prior to admission. He improved

\* This patient was treated at another hospital 18 days before admission for a left lower lobe pneumonia; penicillin was given in dosage of 5000 units intramuscularly every 3 hours and crisis followed. No bacteriologic studies were done. On admission to our hospital, she had a right upper lobe pneumonia and no evidence of her previous lesion on roentgenogram. This is of interest because within a period of about 4 weeks she was treated for 2 attacks of pneumonia by 2 different dosage-interval schedules: first by the multiple small dose method and then by our method. She experienced prompt cure with each method.

TABLE 1.  
Summary of Data in 30 Cases of Pneumonia Treated with Intramuscular Aqueous Penicillin Once a Day

Case No.	Age	Duration of Illness (days)	Degree of Illness	Roentgen Signs	Organisms in Sputum	No. of Injections	Complications	Remarks
1	16	1 to 5	wild mod. acc.	lobar 17 1 lobe 15 2 lobes 1 3 lobes 1 bronchio 1	pneumo. 17 strep. 6 staph. 2 H. influ. 2	4 to 7	asplenia recurrence effusion strang. hernia hepatitis delayed resol.	case of recurrence responded again by crisis to same treatment
2	19 to 26	1 to 7	mild mod. acc.	lobar 7 1 lobe 6 2 lobes 1 central 1	pneumo. 6 strep. 3 staph. 1 H. influ. 1 undet. 1	5 to 13	hepatitis scarlat fever asplenia delayed resol. effusion	1 severe case showed a cavity which disappeared radiographically with complete resolution
3	46	3	moderate	lobar	strep. viridans	11	chronic active glomerulonephritis	complete spontaneous resolution
4	53	3	severe	lobar	pneumo.	2	alcoholic delirium myelitic aneurysm fatty liver	postmortem lung cultures sterile
5	4	4	moderate	lobar	not determined	3	benign nephrosclerosis with hypertensive heart dis. acute pulm. edema	

rapidly with our method of treatment but his temperature fell by lysis. No tubercle bacilli were found in his sputum or pleural fluid. The sputum was not cultured but blood culture on admission was sterile. On discharge he had a thickened pleura.

Group 3 included just 1 case of failure of this therapy. The patient was a 46 year old female who was sick for 3 days before admission. She had a right lower lobe pneumonia and was moderately ill. Her sputum contained *Streptococcus viridans*, although during her 2nd week of hospitalization a pneumococcus appeared. An initial course of 5 injections had no effect and her temperature spiked daily to 103° F. Penicillin was omitted for 2 days and then a 2nd course consisting of 6 injections was given. At this time her temperature reached a low grade level and persisted for several weeks. Chronic active glomerulonephritis was a complication and the pneumonia resolved over a period of 3 weeks. This case conforms to the clinical course of *streptococcus viridans* pneumonia resistant to chemotherapy as reported by Reinhart and Venning.<sup>12</sup>

Group 4 consisted of 2 fatal cases. The first occurred in a 72 year old female who was admitted on the 4th day of illness. She had a typical history of pneumonia and a left lower lobe consolidation was found on physical examination and roentgenogram; her white blood count was 27,000. She had a spastic paraplegia and mild hypertensive heart disease for 15 years. No sputum was obtained but blood culture was sterile on admission. She appeared moderately ill and failed to show improvement on penicillin therapy. On her 3rd hospital day she developed acute pulmonary edema and died 12 hours later. Necropsy revealed mild benign nephrosclerosis, left ventricular hypertrophy and the left lower

lobe pneumonia. Postmortem culture from the involved lobe was sterile.

The second death occurred in a 33 year old male with a history of alcoholism. There was an immediate drop in temperature from 105° F. to normal after the first injection. Delirium then developed with a sharp rise in temperature to 105° F. He became cyanotic and died 36 hours after admission. Blood tests for syphilis were positive, the blood culture was negative on admission and the sputum contained pneumococcus in pure culture. Physical findings and roentgenogram showed a right lower lobe pneumonia which was confirmed at necropsy, and here, too, the postmortem culture from the involved lobe was sterile. In addition, there was a small syphilitic aneurysm of the ascending aorta and a large fatty liver weighing 3200 gm.

To summarize, 30 cases of pneumonia were treated with one daily intramuscular dose of aqueous penicillin-G. Twenty-six cases had pneumococci in the sputum. Eighteen cases (60%) resulted in crisis, 9 (30%) in lysis, 1 failed to respond to treatment (3.3%), and 2 ended in death (6.6%). Two cases (6.6%) had a pleural effusion and 3 cases (10.0%) showed delayed resolution. Postmortem lung cultures were sterile.

**Discussion.** The results compare favorably with those obtained by various investigators<sup>1,3,5,7,10,13,15</sup> in the treatment of pneumococcal pneumonia by the injection of smaller doses at frequent intervals. Comparison of the 2 methods is shown in Table 2. The mortality rates reported in the literature vary between 0 and 18.5% depending on the kind of cases treated. The highest figure was reported by Meads *et al.*<sup>10</sup> for a series of severely ill patients. Kinsman *et al.*<sup>7</sup> reported no mortality in 75 cases, but his patients were soldiers, a youthful group of vig-

orous, well-nourished individuals treated early in the course of the disease. Anderson and Ferguson<sup>1</sup> reported 12.7% in 63 cases of males over the age of 35 years. Dawson and Hobby<sup>3</sup> had 10% deaths in 10 cases. Rotman-Kavka<sup>13</sup> had 8.2% deaths in 170 cases. Tillett *et al.*<sup>15</sup> had 6.5% deaths in 106 cases. Therefore, in 478 cases of pneumonia treated with penicillin by multiple daily doses there was 7% mortality as compared with 6.6% in our small series. In our patients there were no instances of purulent complications but there were 2 cases of pleural effusion (6.6%) and 3 cases of delayed resolution (10%) as shown in Table 2. These figures approximate

From the bacteriologic standpoint, this study is perhaps incomplete in that pneumococci were not typed, but there has arisen a difference of opinion with regard to the need for typing;<sup>16</sup> since the advent of antibiotics many hospitals have ceased typing.<sup>5</sup> It was noted that some patients had a low grade fever for several days after the initial drop in temperature, in the face of symptomatic improvement. This does not seem to bear any relationship to the end-result. This was also noted by Tompsett<sup>16</sup> and by Bunn and his co-workers.<sup>2</sup> The latter used oral penicillin and it was found that a shift to intramuscular penicillin had no effect on this secondary fever. There is no

TABLE 2.

The Effectiveness of One Large Daily Dose of Aqueous Penicillin Compared with the Effectiveness of Multiple Small Doses by the Intramuscular Route

Method	No. of Cases	Mortality %	Pleural Effusion %	Delayed Resolution %
Multiple Doses				
Meads <sup>10</sup>	54	18.5	5.4*	
Kinsman <sup>7</sup>	75	0.0	6.6	0.0
Anderson <sup>1</sup>	63	12.7	11.1	30.1
Dawson <sup>3</sup>	10	10.0		
Rotman-Kavka <sup>13</sup>	170	8.2		
Tillett <sup>15</sup>	106	6.5	1.9	2.8
Total	478	7.0	5.0**	9.0***
300,000 units once a day	30	6.6	6.6	10.0

\* of 37 cases  
 \*\* of 251 cases  
 \*\*\* of 244 cases

the average incidence derived from the few reports in the literature which give data for the older method of treatment: 5% and 9% respectively. The other reports do not mention these complications. However, it may be noted that these comparisons are not strictly valid. Some reports varied as to the type of case, in the amount of penicillin per dose, number of daily doses and the duration of treatment. Nevertheless, in the absence of controls in our series, these statistics are of comparative value.

explanation for this phenomenon except that it may be due to the absorption of pyrogenic products from the area of inflammation.

This report confirms in humans the experimental impression that the effect of penicillin is not dependent on the continuous maintenance of a penicillin level in the blood stream. It appears that the antibacterial effect of the drug outlasts the demonstrable blood level by many hours. This lessens the need for special forms of penicillin having the property of delayed absorption.

Intramuscular doses of 300,000 units aqueous penicillin in man have been shown by McDermott *et al.*<sup>9</sup> to give demonstrable blood levels lasting 4 to 8 hours and this was confirmed recently by Tucker and Eagle<sup>17</sup> for doses of 360,000 units. The question arises as to how penicillin continues to be effective when measurable amounts of the drug are no longer present in the circulation. Parker and Marsh<sup>11</sup> found that after the exposure of staphylococci to penicillin *in vitro*, there is a period during which the surviving organisms do not begin to multiply after the drug is removed. Another factor is the tissue storage of penicillin, for the drug may be retained at the site of infection long after it has disappeared from the blood, as suggested by Tillett *et al.*<sup>14</sup>

The concept of penicillin dose-interval is in the process of change. The blood level is not the only guide for

treatment. Dosage must be based on the therapeutic effect of the antibiotic and take into consideration tissue depots and the bacterial recovery period. Storage varies with the dose of the drug and the tissue under consideration, while bacterial recovery varies with the organism infecting the host.<sup>4</sup> A 3rd factor is, of course, the protective mechanism of the host. In the clinical attack on this problem of dose-interval, the treatment of bacterial pneumonia by the injection of a large dose of aqueous penicillin once a day has been found to be effective.

**Conclusion.** Thirty cases of pneumonia have been treated with a single dose of 300,000 units aqueous penicillin-G intramuscularly once a day with results at least as good as those obtained by smaller doses at more frequent intervals.

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# ISOLATION OF HERPES VIRUS FROM A CASE OF ATYPICAL PNEUMONIA AND ERYTHEMA MULTIFORME EXUDATIVUM

WITH STUDIES OF FOUR ADDITIONAL CASES\*

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During the course of studies on patients with erythema multiforme exudativum associated with pulmonary lesions, attempts were made to isolate an etiological agent. Since the previous observations<sup>4</sup> presented serological evidence suggesting that at least 2 patients might have been infected with a psittacosis-like virus, an agent of this group was sought. Furthermore, since several other investigators<sup>1,2,6</sup> have suggested an etiologic relationship between herpes simplex and erythema multiforme exudativum, the possible isolation of a herpes virus was considered. The results of attempts to isolate viruses from materials obtained from 5 patients and the immunological findings in the sera of these patients are presented in this report.

**Materials and Methods.** *Isolation Studies.* Throat washings in 10% horse serum broth, vesicle fluid from bullous skin lesions, defibrinated blood and/or sputum were obtained from 3 patients who recovered (C.K., R.U., and C.S.). In 2 fatal cases (H.B. and C.L.)† several pieces of lung were taken from the periphery of the lower lobes. Small pieces of the lung tissue were ground in a Waring microblender with enough infusion broth to make 25% or 50% suspensions. These materials were placed promptly in glass ampoules, sealed and stored in the dry ice cabinet until used. In order to

control bacterial contamination, 5 mg. of streptomycin was added per ml. of the throat washings or lung suspensions at the time of inoculation. The materials were inoculated into mice intracerebrally or intraperitoneally and also, in the case of patients R.U. and C.S., on to the chorioallantoic membrane of 10 day old chick embryos.

*Serological Tests.* The tests for cold agglutinins were done by the method previously described.<sup>5</sup> The hemagglutination inhibition test was used for influenza antibodies<sup>7</sup> against the PR8 strain of influenza A and the Lee strain of influenza B. Tests for complement-fixing antibodies for psittacosis and Q fever were done by Dr. Herald R. Cox at the Lederle Laboratories. Tests for neutralizing antibodies against the herpes virus isolated from patient H.B. were done by adding 0.2 ml. of serial 10-fold dilutions of virus-infected mouse brain in 10% rabbit serum broth to 0.2 ml. amounts of the patient's undiluted serum. After standing for one-half hour at room temperature, 0.03 ml. of these mixtures was inoculated into 2½ week old mice by the intracerebral route. The LD<sub>50</sub> of the serum-virus mixtures was thus determined. The neutralizing index for the herpes virus was calculated by dividing the LD<sub>50</sub> of the unknown serum by that obtained when the virus was mixed with normal rabbit serum or with serum of an individual who had no herpetic antibodies.

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† C. K., H. B. and C. L. are listed as Cases 2, 3 and 4, respectively, in a previous paper.<sup>4</sup>

TABLE 1. SUMMARY OF ATTEMPTS TO ISOLATE VIRUSES FROM CASES OF ATYPICAL PNEUMONIA WITH ERYTHEMA MULTIFORME EXUDATIVUM

Case	Material	Animals*	Initial Passage		Subsequent Passages				Result
			Route	Observed, days	No. lived /Total	Internal or Passage	Inoculations	No. lived /Total	
H.B.	50% Lung	Mice	i.c.	16	2/7	7 days 2nd mouse	Mice, i.c. Rabbit cornea	2/8 2/4	Herpetic inclusions in brain. Keratitis in 1; deaths 20 & 21 days; serum neutralizing index of survivors >10,000.
						4th mouse	Suckling mice, i.n.	1/5	Herpetic inclusion in lung.
	50% Lung	Mice, 2½ wk.	i.p. i.c.	16 16	8/8	4th mouse	Eggs, c.a.m.	9/9	All showed lesions typical of herpes.
						—	—	—	Negative.
						—	—	—	Titration in 10-fold dilutions; LD <sub>50</sub> = 10 <sup>-2</sup> , average of 2 tests.
C.L.	25% Lung	Mice	i.c. i.p.	16 16	7/8 7/8	—	—	—	Survivors challenged with HB virus i.c., all died.
C.K.	Sputum	Mice	i.c. i.p.	16 16	7/7 7/7	—	—	—	
						—	—	—	Negative.
C.S.	Throat washing (+ sputum)	Mice, 2½ wk.	i.c.	10	14/16	4 days	Mice, i.c.	13/13	Negative.
		Eggs	i.p.	10	8/8	—	—	—	Negative.
		Mice, 2½ wk	c.a.m.	3	3/3	—	—	—	No lesions.
	Defibrinated blood	Mice, 2½ wk	i.c.	10	8/8	7 days	Mice, i.c.	4/4	Negative.
			i.p.	10	5/6	—	—	—	Negative.
	Vesicle fluid	Mice, 2½ wk.	i.c.	10	7/7	—	—	—	Negative.
R.U.	Vesicle fluid	Mice, 2½ wk.	i.c.	10	10/11	9 days	Mice, i.c. Mice, i.p.	14/14 7/7	Negative.

\* 18-20 g. mice used except 2½ weeks old mice used where indicated.

Abbreviations: i.c. = intracerebral; i.p. = intraperitoneal; i.n. = intranasal; c.a.m. = chorioallantoic membrane.



**Experimental.** *Isolation of a Virus from Patient H.B.* Table 1 presents a summary of the isolation studies. No evidence of the presence of a virus was obtained by the methods used on the materials from 4 of the patients. An agent which killed mice following intracerebral inoculation was obtained from the lung of patient H.B. Intracellular inclusions resembling those found in infections with herpes virus were seen in the brain cells of mice inoculated with this agent.

*Identification of the Virus.* Virus H.B. had the characteristic properties of herpes virus in infection of mice, guinea pigs and rabbits, though it was less active than most strains in producing corneal lesions in the latter animal.

Further proof of the identity of this

Therefore, in its animal pathogenicity, by the character of the lesions that it produced and by its antigenic properties, this agent appeared to be a strain of herpes virus. After the initial isolation, 2 additional aliquots of the frozen lung suspension were titrated in 2½ week old mice, and the virus was found to be present in a titer of  $10^{-2}$ . This suggests that the virus was present in large amounts in this lung.

*Serological Studies.* Antibody studies on patients H.B., C.L. and C.K. have been summarized in the previous report.<sup>4</sup> Cold agglutinins developed in C.K. and H.B. and psittacosis antibodies in C.K. while C.L. showed neither. However, the latter died after being sick for only 5 days. The results of serological studies on patients

TABLE 2. RESULTS OF SEROLOGICAL TESTS IN 2 PATIENTS WITH ATYPICAL PNEUMONIA AND ERYTHEMA MULTIFORME EXUDATIVUM<sup>†</sup>

Case	Days after Onset		Antibody Titers*					
	Respiratory Symptoms	Skin Lesions	Cold Agglutinins	Influenza		Psittacosis	Q Fever	Herpes*
C.S.	8	3	<20	16	4	0	0	2000
	13	8	80	64	8	0	0	—
	20	15	10	32	4	0	0	2000
R.U.	14	8	1280	128	16	0	0	2500
	21	15	2560	256	32	0	0	—
	27	21	—	—	—	0	0	—
	34	28	10	64	10	—	—	2500

<sup>‡</sup> The results of tests done on sera from patients, H.B., C.L. and C.K. have been presented elsewhere.<sup>4</sup>

\* Expressed as reciprocal. † Neutralizing index with H.B. virus.

strain as a herpes virus was readily obtained by serologic tests. It was neutralized by 2 antiherpetic rabbit sera but not by normal rabbit sera nor by rabbit antisera prepared against the viruses of St. Louis or Japanese B encephalitis, lymphocytic choriomeningitis or rabies. Virus H.B. was neutralized by the sera of rabbits and guinea pigs which had survived previous corneal or intracerebral inoculation of this agent. Concentrated globulin prepared from large pools of human sera and convalescent sera from patients in their initial infection with herpes virus also neutralized this virus.

C.S. and R.U. are summarized in Table 2.

Both of these patients showed rising titers of cold agglutinins but neither of them showed antibodies for psittacosis or Q fever. The significance of the slight rise in titer for influenza antibodies is not clear, but since it was demonstrated for both A and B strains, it is probably not specific. Both of these patients had high titers of herpetic antibodies in their sera but no rise in titer was demonstrated. They had both been ill for more than a week when the first specimen was taken and, in addition, C. S. had a previous history

of repeated attacks of herpes labialis.

**Discussion.** Isolation of a strain of herpes virus from the lung of a fatal case of atypical pneumonia with erythema multiforme exudativum is of special interest in light of the discussions of the relationship of herpes virus to the latter disease.<sup>1,2,6</sup> The question of whether this isolation might be due to a fortuitous contamination of the lung of this patient must be raised since this virus is known to have been isolated from the sputum of a patient with atypical pneumonia.<sup>9</sup> The present finding is unusual since, to our knowledge, the isolation of herpes virus from human lung has not previously been reported. In addition, the peripheral lung tissue, even after prolonged storage and considerable handling, was shown to have enough virus to infect mice in a dilution of  $10^{-2}$ . This represents a large amount of virus and therefore it is not likely to be a chance contaminant. Study of sections of this lung, however, failed to show any herpetic inclusions, but patient H.B. had been ill for over 3 weeks so that lesions examined were of considerable age. On the other hand, herpes virus was not isolated from the lung of another fatal case or from sputum, throat washings or vesicle fluid of the 3 patients who recovered. Similar failures have

been reported in this clinical syndrome by others.<sup>2,3</sup>

The techniques utilized here should have allowed for the isolation of most of the agents of the psittacosis-lymphogranuloma venereum group of viruses, so that those agents did not appear to be present in the lungs of the 2 patients tested (H.B., C.L.). However, these patients were not the ones who showed psittacosis antibodies.<sup>4</sup> These isolation experiments, therefore, do not rule out the possibility that one of these viruses may have played a role in other instances of this clinical syndrome.

In C.S. and R.U. high titers of serum neutralizing antibodies for herpes virus were demonstrated. The significance of this observation is difficult to evaluate since most adults show such neutralizing antibodies in their sera with some having neutralizing indices as high as 1000.<sup>8</sup>

**Summary.** A strain of herpes virus has been isolated from the lung of a patient who died with atypical pneumonia and erythema multiforme exudativum. Isolation attempts on the lung obtained from one other fatal case and on sputum, throat washings, blood and vesicle fluid from 2 additional cases gave negative results. The significance of these findings is discussed.

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# PROGRESS OF MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF  
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### THE MERCURIAL DIURETICS

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MERCURY, in its various forms, has been used in many disease states for centuries. The literature on the applications of this element in medicine is, therefore, abundant. A complete review would be of little value, especially since this presentation is concerned primarily with recent publications. Although the material used herein is derived largely from the literature of the English speaking countries, some significant foreign articles are included.

The use of mercury as a diuretic is of remote date, references to its use for this purpose having been made by Paracelsus as early as the sixteenth century.<sup>63,141</sup> Crawford and McIntosh<sup>29</sup> referred to a statement in 1799 by Ferriar that the diuretic action of digitalis was increased when calomel was added. The texts of the early nineteenth century refer to the combined use of digitalis and mercury.<sup>23,37,44,57</sup> Digitalis, squill and calomel were included in Guy's Hospital pills.<sup>63</sup> However, the overenthusiastic use of mercury resulted in

undesirable reactions so that it fell into disfavor for a time, until Jendrassik<sup>77</sup> in 1885 renewed interest in the use of mercurous chloride in the management of cardiac edema.

The first organic mercurial employed to induce diuresis was novasurol (the double salt of sodium mercurichlorophenyl-oxyacetate with diethyl barbituric acid), introduced originally as an antisypilitic agent in 1917.<sup>108,133</sup> Three years later Saxl and Heilig<sup>125</sup> reported the effectiveness of this compound as a diuretic. After administration of novasurol, they observed a diuresis when all other measures failed. Brunn<sup>16</sup> introduced salyrgan (mersalyl) (sodium [O (Hydroxy-mercuric-methoxyl-propyl-carbamyl) phenoxy] acetate) in 1924. Neptal<sup>105</sup> and mercupurin (sodium trimethyl - cyclopentane - dicarbonic acid - methoxy - mercury - allylamide-theophylline)<sup>133</sup> were subsequently described; mercuhydrin (sodium salt of methoxyoximercuripropylsuccinylurea with theophylline) is the latest of the organic mercurial diuretics to appear.

CHEMISTRY AND PHYSICS: Whether mercury is administered as an inorganic or organic compound, its diuretic effect is probably due to the mercuric ion.<sup>134</sup> In the former group of compounds, ionization is greater; in the latter, mercury is combined more or less firmly into an organic complex so that it ionizes only slightly. Differences in ionization between the inorganic and organic compounds are responsible in part for the variations in absorption, local effects and toxicity, the latter phenomenon being more active with greater ionization.

<sup>3</sup> The local effect of mercury depends largely upon the concentration of mercuric ions. Proteins in low concentrations are precipitated but may redissolve in excess of proteins; such a state always exists in the body in the presence of therapeutic amounts of mercury. The chemical environment of the body influences greatly the physical and chemical reactions of this element;<sup>133,140</sup> for example, the halides, amides, alkalis and acids affect the phenomena of ionization, deposition, and physical diffusion. Details of these actions may be found in the paper by Taylor and Young.<sup>140</sup>

The action of any particular compound of mercury is influenced by its solubility. Mercuric chloride is less ionized than mercurous chloride,<sup>140</sup> although the former is more soluble. However, its ability to replace rapidly mercuric ions removed from a solution of mercuric chloride results in its acting as a highly ionized compound.

Although the less ionizable compounds may diffuse through membranes as whole molecular structures rather than as ions,<sup>140</sup> ionic diffusion of mercury is more rapid than molecular diffusion. Since the manner in which mercury is "metabolized" by the body is partially dependent upon diffusion across the cellular membranes, the rate and degree of ionization determine in

part the rate with which mercury reacts in the organism. The effect *in vitro* of varying chemical environments on diffusion of several inorganic and organic compounds of mercury was studied by Taylor and Young.<sup>140</sup> They found that hydrochloric acid, calcium chloride and ammonium chloride increased the rate of diffusion of the mercury of inorganic compounds such as mercuric chloride, mercurous chloride and mercuric succinamide. An excess of hydroxyl ions was without appreciable effect on these inorganic compounds but increased the rate of diffusion of the mercury of organic compounds. Thus, organic mercurial compounds which exhibit little diffusion into water may diffuse readily in an environment such as that of a living cell. Potassium iodide, on the other hand, enhanced diffusion of both inorganic and organic compounds, supposedly because of the formation of a potassium mercuritetraiodide, which diffuses most readily in distilled water. Ammonium chloride greatly augmented diffusion of the mercury of salyrgan and novasurol. The mercury of organic compounds diffuses across semipermeable membranes into blood serum. This may be related to the fact that metallic mercury and inorganic mercurial salts are more soluble in serum than in water, a phenomenon of biologic significance.

Since the introduction of British anti-lewisite (2,3-dimercaptopropanol) by Peters and associates,<sup>114</sup> numerous publications have indicated the importance of the reaction between mercury, and other heavy metals, and the thiol groups of BAL as well as those of the other thiol-containing compounds.<sup>12,25,38,58,92,93,97,121,149</sup> This type of reaction is of importance, not only in therapy but also for a better appreciation of the pharmacodynamics of mercury.

One difficulty encountered in the

study of the metabolism of mercury has been the relative insensitivity or cumbersome nature of chemical analyses for this element. Many methods of analysis have been described, most of which involve digestion of the organic material in the presence of reducing agents. This latter procedure entails a loss of mercury which in some cases may amount to as much as 75%.<sup>154</sup> Furthermore, many chemical methods are not sensitive to small amounts of mercury.<sup>30,56</sup> With a normal daily dietary intake of about 20 micrograms of mercury and the urinary and fecal excretion of about 12 micrograms,<sup>133</sup> chemical determinations become difficult. This difficulty is better appreciated when it is realized that only a small amount of mercury is contained in the organic compounds used as diuretics. The amount of mercury and the manner in which it is bound in these compounds vary slightly. For example, mercuzanthin (mercurphylline) contains 37 to 42% mercury by weight, salyrgan 37 to 42% mercury by weight, and mercurhydrin 39 mg. per cc.<sup>107</sup>

**PHARMACODYNAMICS:** (a) *Absorption.* The absorption of mercury may occur by many routes: respiratory tract, skin, gastrointestinal tract, vagina, rectum, and interstitial tissues. Poisoning by inhalation as well as by vaginal and rectal use of mercurial compounds has long been recognized.<sup>56,133</sup> Absorption may occur anywhere along the gastrointestinal tract. Significant amounts of mercury have been found in the blood of dogs within 10 minutes after the introduction of bichloride of mercury into the stomach;<sup>18</sup> shorter periods of time sufficed when large doses were administered. Mercury has been recovered in the urine 6 to 12 hours after ingestion of calomel.<sup>56</sup> The bichloride of mercury is more rapidly absorbed from the intestine. Metallic mercury and mercurous chloride may be oxidized to the mercuric form before

absorption, but it is possible that there is molecular transfer of mercurous chloride across cellular membranes. When the organic mercurial diuretics are administered by rectal suppository, diuresis ensues within 1 to 3 hours.<sup>52</sup> However, there is considerable variation in the amount of mercury absorbed by this route as measured by the mercurial content of the wall of the colon and of the urine.<sup>14</sup>

Mercurial diuretics are most commonly administered parenterally. Absorption from muscle is more rapid than from subcutaneous tissue and is poorest from adipose tissue. Sloughs may occur in the latter two tissues as a result of local action of mercury. The factors governing the rate of absorption following intramuscular injection were investigated by DeGraff and his coworkers.<sup>30</sup> They demonstrated that the organic mercurials which did not contain theophylline caused greater local reaction than those which did. Urinary excretion of mercury, from which absorption may be estimated, accounts for only part of the injected dose. When organic mercurials (mercurpurin and salyrgan with and without theophylline) were injected intramuscularly and the muscle was removed at varying intervals of time, it was found that absorption was most rapid immediately after injection.<sup>30</sup> When theophylline was absent, there was 10 to 20% of the injected mercury remaining at the site of injection 39 to 48 hours later, whereas when theophylline was added in amounts up to 5% of the total organic mercurial diuretic, absorption was almost complete by the end of one hour. The chemical method used in these studies for the determination of mercury had a 10 to 15% error. Organic mercurials injected into the ascitic fluid have been followed by untoward reactions,<sup>69,108</sup> and this route would therefore seem to offer no advantage over intramuscular injection.

(b) *Distribution.* After mercury enters the blood stream from any site of administration, it combines in large part with the plasma albumin to form an albuminate.<sup>27,74,80</sup> The strong affinity of albumin for the mercurials resides in a single SH group present in the albumin molecule.<sup>75</sup> In spite of this, tracer studies of the regression curves of mercurhydrin labeled with radioactive mercury and administered intravenously show that the mercury leaves the blood stream rapidly.<sup>143</sup> It is widely distributed throughout the body, being found in almost every organ, including bone.<sup>86</sup> It occurs in greatest concentration in the kidneys, although the liver contains about three times as much, by virtue of differences in the size of these organs. As previously stated, the relatively insensitive chemical analyses used for mercury encumber the evaluation of small amounts found in various organs and body fluids. This problem is being attacked by the use of radio-mercury. Mercury has reportedly been found in plasma and in the washings from red blood cells, though the validity of the results is questionable, since in some instances no mercury was found in the whole blood.<sup>18</sup> Its presence in spinal fluid is controversial; some investigators were unable to find even a trace in the spinal fluid of patients treated by inunction or injection, or even in patients with fatal mercurial poisoning.<sup>151</sup> Ascitic fluid and saliva have been found to contain small amounts of mercury,<sup>86,151</sup> and greater quantities are present in bile.<sup>80</sup>

Tissue sections of liver and kidney have been treated with hydrogen sulfide to demonstrate the presence of mercury. When dogs were given a toxic dose of a mercuric chloride and tissue sections of the kidneys were treated with hydrogen sulfide, black granules were seen in the arterioles, capillaries, lymphatic spaces, tubular cells and in white blood cells present in the kidney.<sup>18</sup> When liver sections were

treated in this manner, the granules of mercuric sulfide were found in the lumen of the central veins, in the walls of the veins, and in the connective tissue of the periportal fields. No granules were noted in the parenchymal cells, although some were present in Kupffer cells and in the epithelium of the large bile ducts.

The form in which mercury is retained or stored by the tissues is unknown. It has been suggested that it is stored in combination with protein.<sup>136</sup> The quantity and type of mercury administered, whether highly or slightly ionized, organic or inorganic, and the specific chemical environment determine the amount stored and the specific tissue affinity.<sup>133</sup> The storage equilibrium is affected by acid and alkaline precursors. As is the case with lead, the amount stored is increased by a high pH.<sup>140</sup>

(c) *Excretion.* The chemical form in which mercury is excreted is unknown. In the case of ionizable mercury, such as mercuric chloride, the excreted compound might differ from that resulting from administration of mercuric salicylate and the poorly ionized organic compounds. It has been postulated that a mercurial compound may be absorbed and excreted as such,<sup>86</sup> but this has not been definitely established.

There are several avenues of excretion of mercury, the most important of which is by way of the urine. Excretion in the feces occurs by way of the bile and the intestinal mucosal and salivary glands. Bile contains a higher concentration of mercury than does the blood.<sup>133</sup> Mercury is present in milk and sweat, but in inconsiderably small amounts.

The excretion pattern of mercury administered over a long period of time by inunction or injection to the point of "saturation" will differ from that following administration of a single dose for its diuretic effect. When

the body is "saturated", the concentration of mercury in the urine approximately equals that in the blood.<sup>133</sup> However, it is the concentration of the circulating mercury which determines the rate of excretion, especially in the urine.<sup>136</sup> During therapeutic administration by inunction, the blood level obtained is usually 1 to 2 and not over 3 mg. per liter, whereas the biliary concentration is higher but variable. Excretion studies of mercury following prolonged periods of administration were reported in detail by Lomholt.<sup>90</sup> With prolonged administration of mercury by inunction or injection, excretion may continue for 6 months after cessation of treatment, indicating that mercury has been accumulated and stored in the body.<sup>86,133,136</sup> On the other hand, after a single intravenous injection, as in diuretic therapy, excretion has been reported to be complete in 48 to 72 hours, 75% or more of the injected mercury being recovered in the urine and feces within this period.<sup>133</sup> Kwit and associates<sup>87</sup> and Gold<sup>91</sup> reported that the mercury of organic mercurial diuretics is completely eliminated in 24 hours or less if satisfactory diuresis is maintained. Modell<sup>91</sup> pointed out that this might not be true in the presence of oliguria. It is exceedingly difficult to recover 100% of the injected dose of mercury by chemical methods. In fact, the percentage excreted after a single injection has not been definitely established.

The time required for excretion varies, with the type of compound administered and the route of administration.<sup>133</sup> A more rapid rate of excretion follows intravenous than intramuscular injection. The poorly ionized organic compounds are eliminated more slowly than the more highly ionized inorganic ones with both of these routes of administration. The tendency to retain mercury in the body is least following intravenous injection

and greatest following intramuscular injection of a suspension of metallic mercury in oil.<sup>86</sup> The rate of elimination of most mercurial preparations is greatest immediately after administration.<sup>30</sup> DeGraff and his associates<sup>31</sup> found that theophylline increased excretion by 30 to 40% after intramuscular and intravenous injection. Since various chemical environments influence ionization, storage equilibrium and physical diffusion of mercury, it is to be expected that elimination of mercury by all pathways will vary considerably from one individual to another and with time in the same individual.<sup>140</sup>

(d) *Active Principle.* The mercuric ion exerts many effects on the body, but that which primarily concerns us for the moment is its diuretic effect on the kidney. This action of ionizable forms of mercury has been shown to be great. Organic and inorganic mercurials and colloidal mercury act similarly.<sup>134,135</sup> The diuretic effect of organic mercurials has been attributed to the mercury released from these compounds. On the basis of the amount of parenterally administered mercury, the ionizable inorganic compounds are superior.<sup>134</sup> Melville and Stehle<sup>100</sup> concluded that the action of mercuric chloride was identical with that of novasurol except for the duration of the latent period before the onset of diuresis. Since the diuretic effect depends upon the availability of free mercury, the tissues and body fluids apparently release mercury from local organic combination during this latent period.<sup>91,134</sup>

(e) *Site of Action.* The precise mechanism by which mercurial diuresis is effected is unknown. The existence of some extrarenal effect in the response has neither been established nor excluded. Saxl and Heilig<sup>125,126</sup> were of the opinion that some extrarenal actions were involved on the basis of

refractometer and chemical studies on the blood immediately following injection of a mercurial. Others demonstrated hemodilution in the first few hours.<sup>29,130</sup> DeVries<sup>36</sup> observed that mercurial diuresis in the presence of edema was not accompanied by changes in protein and hemoglobin concentration, whereas these values increased in the absence of edema. Schmitz,<sup>129</sup> on the other hand, found no indication of hemodilution nor any evidence that diuresis was preceded by mobilization of fluids from tissue spaces. Furthermore, the administration of sodium chloride resulted in a decrease in the refractive index without an associated increase in diuresis or in the rate of glomerular filtration.<sup>128</sup> These observations were interpreted to indicate renal action of the mercurials. Bryan and his associates<sup>17</sup> found no consistent change in specific gravity or colloidal osmotic pressure immediately after the injection of mercury, but during diuresis there was hemoconcentration.

The work of Bartram<sup>2</sup> and of Christian and Bartram<sup>26</sup> seems to establish that the major, if not the sole, action of mercury is limited to the kidney. By injecting small amounts of novasurol and salyrgan into one renal artery, they produced typical diuresis from the injected kidney, whereas the urine of the other kidney remained unchanged as to rate of excretion and character. The urine from the injected kidney was pale, of low specific gravity, and contained albumin. When the amount of mercury injected was increased, bilateral diuresis occurred, but its onset was earlier on the injected side. With injection of extremely large amounts, there was a toxic reduction in rate of urinary flow from the injected side and typical mercurial diuresis from the opposite kidney.

Govaerts<sup>61</sup> injected an animal with

mercurial diuretic and at the height of diuresis transplanted one of its kidneys into the neck of an untreated animal. The transplanted kidney continued to form pale urine of low specific gravity as it had done in the injected animal. This experiment indicates that it is possible for the diuretic action of mercury to be produced by renal action alone but does not exclude contributing systemic factors. However, the observation by Keith<sup>83</sup> that mercury will not cause diuresis in the presence of low plasma chlorides makes it difficult to exclude extrarenal effects completely. In addition, observations have been made in man, by biologic titration, on the inhibitory effects of pitressin and of desoxycorticosterone acetate on mercurial diuretics. Reactions such as these may influence mercurial diuresis.

(f) *Mode of Action.* The precise mechanism by which mercury acts upon the kidney is unknown. Various investigators<sup>9,38,72,128,148</sup> have shown that there is no increase in glomerular filtration but that diuresis is due to decreased rate of tubular reabsorption. Mercury does not alter the ability of the kidney to secrete urea.<sup>112</sup> Richards,<sup>120</sup> working with frog kidney, found that mercuric chloride "abolished the power of active reabsorption and power of selective retention of diffusible substances by the renal tubule."

As indicated previously, the specific action of mercury on the tubule is unknown. Mercury is a protoplasmic poison, and its diuretic effect has been considered by some to indicate a mild toxic action on the renal tubular cells.<sup>146</sup> It is possible that mercury interferes with certain enzymatic systems within them. Mercuric chloride prevents glycolysis in frog muscle extract,<sup>56</sup> but when monothiols, such as cysteine and glutathione, were added, glycolysis was reinitiated. Mercury has been shown to prevent the rat kidneys



from acting as a source of blood sugar, whereas ureteral ligation and phloridzinization did not prevent gluconeogenesis in the kidney.<sup>119</sup>

Gilman and his coworkers<sup>58</sup> studied the effects of BAL, BAL glucoside and thiosorbital on acute mercurial poisoning. They were able to protect the animals from a uniformly fatal dose of mercuric chloride with all three thiols. Since early treatment completely protected the animals, the authors concluded that the mercaptides formed *in vivo* are sufficiently non-dissociated to prevent combination of the mercuric ions with cellular enzymes. It was also found that mercury could be removed from intracellular combination by delayed administration of thiols. This is in agreement with the experience of Longcope and Luetscher<sup>93</sup> and of Ginzler.<sup>60</sup> The mercury-BAL complexes are in themselves toxic.<sup>58,66</sup> With BAL it is possible to prevent or arrest mercurial diuresis promptly;<sup>38,45,66,97</sup> this is also true for chloruresis. Another injection of a mercurial will reinstitute diuresis, which may again be counteracted by BAL.<sup>66</sup>

Immediate reduction in the volume of the kidney, with concomitant reduction in renal blood flow, has been recorded after an intravenous injection of a mercurial diuretic.<sup>21,15,76</sup> This lasts 5 to 10 minutes and is accompanied by decreased urinary output. BAL, cysteine and glutathione prevented any diminution in the volume of the kidney. The monothiols did not reduce diuresis in these studies, whereas BAL completely inhibited it.

**PHYSIOLOGIC RESPONSE:** Diuresis resulting from administration of mercury causes certain chemical and physical changes in the blood. There is a reduction in blood chlorides.<sup>10,29,63,108</sup> Hemodilution and hemoconcentration are inconstant findings.<sup>10,29,63,91,125</sup> The total serum base is lowered, although this value may return to

normal 24 hours later.<sup>68</sup> Blood urea is not significantly altered.<sup>17</sup>

Changes in urine are much more pronounced. All investigators agree that the urinary excretion of chloride is greatly increased.<sup>9,29,42,77,81,82,108,122,126</sup> If the amount of mercury administered is excessive, excretion of chloride will diminish,<sup>122</sup> but such a dosage scheme is out of the range generally employed therapeutically in man. Blumgart and his associates<sup>9</sup> observed an increase in the excretion of chlorides, sodium, potassium and calcium in comparatively constant relationships. Others have reported greater excretion of sodium especially when sodium intake was unrestricted.<sup>65,68,81,82,108,118</sup> In normal individuals, the output of chloride, sodium, potassium and calcium fall below the normal or control level, a compensatory positive balance, for 2 to 3 days after diuresis. Inorganic sulfates and phosphates are not particularly affected by mercurial diuresis.<sup>9</sup> Such changes as may occur in the protein content of the urine are difficult to evaluate, since the methods of analysis usually employed were not sufficiently sensitive.

The specific gravity of the urine is lowered during mercurial diuresis. This is to be expected, since tubular reabsorption of the glomerular filtrate is decreased. The volume of urine and its specific gravity vary widely with different preparations of mercury, routes of administration, and degrees of hydration and edema. Various maximum values were reported, ranging from 1 or 2 liters to as much as 14 liters following administration of a single dose.<sup>133</sup> The duration of diuresis varies from 8 to 48 hours, but it usually lasts less than 24.

**TOXICITY:** The mercuric ion exerts widespread toxic effects. Lesions which have received greatest attention are those in the kidney, colon and liver. The findings in mercurial poisoning in man and other mammals are identical.

The basic renal lesion is represented by degenerative and necrotic changes in the tubular epithelium.<sup>18,39,49,71,79,96,102,127,139</sup> Calcium may be deposited in necrotic tubular cells within a week after poisoning. Renal changes may appear within a few minutes after intravenous injection.<sup>101</sup> Glomerular changes have also been described.<sup>96</sup> Histologic studies of the human kidney following intravenous administration of mercury disclosed changes resembling mild mercurial poisoning.<sup>67,123,147</sup> After death from another cause sections of the kidney in a subject poisoned with salyrgan revealed complete recovery from the renal injury.<sup>35</sup> Roby and Pfeiffer<sup>122</sup> demonstrated that renal injury usually results when the blood level of mercury exceeds certain levels, which vary with the mercurial compounds. It is well to note that injury limits the ability of the kidney to excrete mercury.<sup>86</sup> Casts and cell counts have been found to be elevated in the urine of rats following administration of a dose of .0008 gm. of mercury per kilogram of body weight, the usual clinical dose for man.<sup>15</sup> Because of relatively few studies of this kind in man, conclusions concerning human toxicity are extremely limited.

Histologic examinations of the liver following mercurial intoxication revealed degenerative changes and congestion of the blood vessels and sinusoids. Hemosiderin may be deposited in the parenchyma.

Mercury has serious effects on the cardiovascular system. Reference has been made to the vasoconstriction occurring immediately after the intravenous injection of mercury.<sup>24,45,76</sup> Salant<sup>124</sup> found that small amounts of mercury, 1 part in 100,000 Ringer's solution, produced heart block and delirium cordis in the turtle. These disturbances sometimes followed concentrations as low as 1 part in 10,000,000. Cardiac standstill of 1 to 3 minutes duration

and extreme reduction in blood pressure were observed in dogs when mercuric succinate, benzoate or acetate were employed. Johnston<sup>78</sup> studied the effects of salyrgan and mercupurin as well as mercurous and mercuric chloride on the turtle heart. He found that the organic mercurials were just as toxic as the inorganic ones when their mercurial content was compared; purine derivatives decreased this toxicity. Sodium thiosulfate restored the cardiac mechanisms to normal. By using magnesium sulfate in conjunction with the mercurial, Pines and his coworkers<sup>115</sup> were able to reduce the incidence of ventricular fibrillation in dogs caused by esidrone (the sodium salt of pyridenedicarboxyl- $\beta$ -mercuri- $\alpha$ -hydroxypropylamide-theophylline). It did not protect against disturbances in conduction, however. A number of electrocardiographic studies have revealed mechanical disturbances and various degrees of atrioventricular and intraventricular block.<sup>8,22,89,153</sup> Premature beats were relatively common. Long and Farah<sup>91,92</sup> and Farah and Maresh<sup>45</sup> investigated the ability of the dithiols and monothiols to prevent cardiovascular reactions to mercury. Cardiac failure produced by salyrgan in a heart-lung preparation was reversed by the thiols. The 50% lethal dose for mice was increased from 103 mg. to 176 mg. of salyrgan per kg. of body weight by the thiols. The vasoconstriction which immediately follows an intravenous injection was abolished by these antagonistic drugs.

The immediate fatalities which occur after intravenous injection of organic mercurial diuretics result from the toxic action of mercury on the heart. The literature on this subject was recently reviewed by Kaufman,<sup>80</sup> who reported a fatality and reviewed 31 others. Another case has since been reported<sup>111</sup> and there are undoubtedly many others. Certain factors are im-

pressive in these fatal cases. First, the dosage given to the children was large. Second, a large percentage of the fatalities occurred in patients with nephrosis and nephritis. Third, in some cases there were premonitory signs of toxic reaction; in some, death followed the first injection; and in others the mercurial had been well tolerated for long periods of time before the fatal reaction occurred. Fourth, the time from injection to death is very short, usually 2 to 3 minutes and not more than 5. Undue apprehension, dyspnea, substernal discomfort, sweating, pallor, and changes in pulse should be considered as warning signs.<sup>150</sup> A number of alarming nonfatal reactions have been observed.<sup>1,20,144</sup> Certain generalized systemic reactions to mercury may occur somewhat later: chills, fever, asthma, and cutaneous manifestations of hypersensitivity to mercury.<sup>6,19,50,81</sup> Another delayed reaction is overdehydration with excessive loss of electrolytes and fluid. The syndrome of weakness, restlessness, apathy, mental confusion and possibly coma resulting from overdehydration and electrolyte imbalance has been emphasized by Poll and Stern<sup>116,117</sup> and by others.<sup>32,35</sup> Administration of fluid and electrolytes, particularly sodium, will correct the underlying fault. Tetany following administration of mercurials has also been reported.<sup>38</sup>

Prevention of toxic reactions is difficult and in certain cases probably impossible. If a patient manifests reactions to intravenous injection of diuretics, this route of administration should be discontinued. Many reactions can be averted by the use of the intramuscular route, for which there are no reported deaths and only one serious reaction.<sup>73</sup> The speed with which an injection is given is also important, as is the total amount administered.

The question of chronic damage of

the renal tubules from repeated use of mercurial diuretics often arises. However, there are numerous reports of patients who have received extremely large quantities of organic mercurials over long periods of time without any evidence of renal injury by histologic examination or by renal function tests.<sup>16,51,88,95,109,110,131,152</sup> Maxwell and his associates<sup>99</sup> were unable to detect any histologic differences between the kidneys of patients with congestive heart failure treated with mercurials and those who had received no mercurial diuretics.

**CLINICAL APPLICATIONS:** The essential indication for the use of mercurial diuretics is the need to reduce the extracellular fluid compartment, especially in congestive heart failure. It is not necessary in this review to discuss the mechanism of retention of electrolytes and water in edematous states. Regardless of the precise mechanism, there is retention of sodium and, therefore, water. Mercurial diuretics increase the rate of excretion of water and sodium.<sup>61,68,81,82,108,118,142</sup> When symptoms result from an increase in extracellular fluid, a mercurial diuretic is indicated to remove this fluid and to prevent its recurrence, unless circumstances preclude its use.

Since novasurol was introduced in 1920,<sup>125</sup> mercurial diuretics have been employed with varying popularity in the management of congestive heart failure, but more recently they have received much greater attention. The more vigorous attack by these agents is the result of the efforts of a large number of clinical investigators, chiefly Gold and his associates.<sup>60,61</sup> The method of trial and error must be used in order to establish a maintenance dose for each individual. Initially, when the patient is in severe congestive failure, mercurials may be used more frequently; that is, daily or every other day, until sufficient dehydration has

been achieved and body weight has been stabilized. The dosage necessary for this may vary from 0.5 cc. weekly to 2 cc. daily of mercurhydrin, mercupurin or salyrgan with theophylline. Dosage levels of 2 cc. daily may be far too great for most patients. Weight loss should not exceed 2 to 3 pounds daily. Too rapid reduction in weight by over-enthusiastic treatment may cause over-dehydration and electrolyte imbalance of serious nature. The stabilized weight level has been defined as the "dry weight" for that particular individual,<sup>60</sup> the size and frequency of subsequent doses varying to maintain this weight. It is preferable, therefore, to administer the smallest dose which will produce the desired amount of diuresis than to employ the same dose, 2 cc., empirically for every patient. The less used, the less is the likelihood of toxic reaction. Modell<sup>103</sup> found that 2 small doses administered weekly often effect a greater loss in weight per volume of diuretic than the same amount of material given once weekly. The former method is more desirable, since a stationary level is more nearly maintained and unfavorable reactions are less probable. It is wiser to prevent reaccumulation of fluid than to permit large volumes of fluid to collect and symptoms to return. Paroxysmal nocturnal dyspnea may be prevented by the use of mercurial diuretics, but mercurials alone are rarely indicated for this.<sup>132</sup>

Except in early and mild failure, the management of chronic congestive heart failure should include mercurial diuretics in addition to digitalis. If the use of diuretics is reserved solely for the more severely ill patients who do not respond satisfactorily to digitalis alone, the time required for the less serious patients with cardiac failure to achieve a state of compensation or maximum improvement is lengthened. Mild and moderate degrees of congestive heart failure may be managed by the use of

mercurial diuretics alone, but in the absence of digitalis the maintenance dose of the mercurial is higher. It has been adequately demonstrated that digitalis increases the cardiac output and therefore the renal blood flow. It is likely that the mercurial diuretics will effect greater diuresis when the renal blood flow is more nearly normal. It is important to realize that mercurial diuretics constitute only one aspect of the relatively complex system and the many factors concerned with the management of congestive heart failure. A detailed discussion of the management of heart failure will not be presented here.

The intravenous and intramuscular routes of administration are equally effective except in extreme circulatory collapse, when the latter is less certain. However, since the intramuscular route is not attended by the danger of immediate reactions, it is preferable. The injectable preparations, salyrgan with theophylline, mercuzanthin and mercurhydrin, may be given either intravenously or intramuscularly. In the presence of theophylline the reaction at the site of intramuscular injection is reduced and the rate of absorption is increased,<sup>30</sup> but still some unpleasant local reactions may occur. Mercurhydrin appears to cause less local tissue reaction and less pain at the site of the injection.

The effectiveness of mercurial diuretics administered orally has been investigated by Batterman and his associates<sup>3,4,5</sup> and by Borg.<sup>11</sup> The tablets were given in a large single dose as well as in multiple small doses; the latter was more efficient in causing diuresis. A loss of over 3 pounds in weight occurred in 60 to 70% of the trials. This method of administration is not as effective or dependable, however, as the parenteral route. Large oral doses are sometimes required to induce diuresis. Nausea, vomiting, and diarrhea

occur frequently. If it is well tolerated and if the response is good, oral administration offers certain advantages in the ambulatory patient.

Administration of mercurials by rectal suppository has been investigated.<sup>13,14,21,34,48,113</sup> It has produced diuresis in 50 to 70% of trials. However, the incidence of rectal irritation by suppositories containing mercurials is too high to justify advocacy of this route.

Numerous studies have been carried out on the relative efficacy of the various mercurial preparations available for clinical use.<sup>28,33,43,47,53,62,104</sup> Those containing theophylline proved more effective than the theophylline-free diuretics. There appear to be no significant differences in the diuresis resulting from the various commercial preparations, all of which contain theophylline.

The influence of ammonium chloride and other acid-producing salts on the effect of mercurial diuretics has been reported by numerous investigators.<sup>7,33,34,40,41,43,47,48,54,61,70,113,137,145</sup> There is general agreement that the diuretic effect of the mercurials, whether administered orally, rectally or parenterally, is enhanced to varying degrees by premedication with ammonium chloride and other acid-salts. Since ammonium chloride must be used in large doses to be effective, gastrointestinal symptoms are frequently encountered. The magnitude of the increase in diuresis does not usually justify the precipitation of nausea, vomiting and abdominal pain in an already seriously ill patient. There appears to be no need for the acid-producing salts in the usual instance, the mercurials alone being adequate. In certain selected cases where potentiation of diuresis is essential, ammonium chloride may be tried. It is well known that ammonium chloride alone is a mild diuretic.

Gratifying results have been achieved in congestive heart failure with the use

of mercurial diuretics. The symptoms caused by an increase in the volume of extracellular fluid are relieved. Paroxysmal nocturnal dyspnea may be prevented by maintenance doses. The life expectancy in many patients with congestive heart failure is considerably lengthened, and the duration of individual episodes of decompensation is shortened. Ascites may be controlled, so that abdominal paracenteses are rarely necessary. The edema of the nephrotic syndrome likewise may be controlled. However, renal function must be carefully observed when mercurials are employed to combat renal edema. Edema as a result of thrombophlebitis and lymphatic disease may diminish after administration of mercurials. Inflammatory edema and ascites associated with abdominal malignancy respond poorly if at all. Although ascites associated with hepatic cirrhosis frequently responds well, this treatment should be employed cautiously in this state.

**CONTRAINDICATIONS:** There are certain contraindications to the use of mercurials, for example, the presence of acute glomerulonephritis. The presence of renal disease with insufficiency prohibits the use of mercurials, since the excretion of the injected mercury is delayed and accumulation is possible. Nevertheless, an elevation of the urea nitrogen may result from congestive heart failure without primary renal disease.<sup>102</sup> Obviously, the presence of moderate elevation of blood urea nitrogen with albuminuria is not necessarily a contraindication. If, however, the blood urea nitrogen is over 60 mg. per 100 cc., mercurials should not be used.

Known idiosyncrasy of the patient to mercurials contraindicates their use. Severe reactions to intravenous injections preclude further use of this route of administration and only small doses should be given by any other route.

Other contraindications include inadequate response to injections of the mercurial diuretics, or oliguria, hematuria, severe albuminuria in patients previously normal urine, overdehydration and depletion of electrolytes, at least until these states have been corrected. Further diuresis should not be attempt-

ed when mobilization of large amounts of fluid of edema has resulted in evidence of digitalis intoxication. Following some of the less severe reactions, use of mercurial diuretics may be resumed in smaller amounts and at longer intervals of time, but careful observation of the patient is imperative.

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# NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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## RELIGION AND PSYCHIATRY

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FOR many centuries religion and medicine were so closely related that temples were not only religious altars but also healing shrines.<sup>36</sup> The religious mentor was also the physician.<sup>7,34</sup> However, with the development of science, medicine and religion assumed distinctive roles in society.<sup>9,31,46</sup> Religion must concern itself primarily with the goals and values of life, whereas science concerns itself primarily with the facts and means of life.<sup>28</sup> The sick room is rightfully considered the domain of both physician and minister, as each is equally interested in the welfare of the individual. Psychiatry is a branch of medicine and is not a philosophy of life.<sup>27</sup> The goals of religion and psychiatry are very similar in many areas.<sup>5,24</sup> Both recognize the family as a powerful influence on a child's development and ultimate social adjustment.<sup>2</sup> Both share the common aim of human betterment.<sup>31</sup> Both rejoice when the individual adopts a healthy and happy philosophy of life and is able to be tolerant of the shortcomings of others.<sup>20,27</sup>

Religion is, without a doubt, one of the chief supports in the emotional adjustment of the vast majority of people. It is a source of comfort, reassurance and hope.<sup>32</sup> From the scientific standpoint alone, a healthy accept-

ance of religion is a major factor of good mental hygiene. During World War II, psychiatrists and chaplains, as staff officers, often found themselves working on similar problems, especially those relating to morale, combat efficiency of troops, and so on. It was found, for example, that a firm abiding faith in God was a strong bulwark against the development of severe incapacitating combat-induced anxiety in many men.<sup>17,32</sup> It was a common phenomenon in amphibious combat units for attendance at religious services to increase markedly as the fateful "D-Day" approached.

The past few years have seen an increasing interest in and utilization of the principles of dynamic psychology by clergymen. Rabbi Joshua L. Liebman,<sup>27</sup> in his excellent book, "Peace of Mind," states that "Psychology must not be viewed as a competitor of religion, any more than the science of optics should be regarded as a competitor of normal vision. The fact that the sanctuary has its unique contribution to make to the world does not mean that it should refuse the helpful hand of a great ally—the psychological clinic." John S. Bonnell,<sup>4</sup> in his recent book, "Psychology for Pastor and People," states that "It will be of inestimable gain to the Christian Church when

highly-trained pastors are available in all parts of the nation: men who have not only a thorough grounding in psychology and in the basic principles of psychiatry but in addition a clinical or hospital training." Many theological schools do arrange for "internships" for their students in psychiatric hospitals.<sup>42</sup> The Federal Council of Churches of Christ in America has taken active leadership in presenting mental hygiene to clergymen in special conferences.<sup>31</sup> Ministers who have had the opportunity of working with psychiatrists have given abundant written testimony of their experiences. For example, one clergyman<sup>3</sup> asserts that "The harmonious interrelationships of ministers and medical men can best be achieved when both realize that, while each has a distinct function to fulfill, their ministrations overlap, and the effectiveness of each is enhanced by working in harmony with the other."<sup>30</sup> Carrol A. Wise<sup>44</sup> says that it is "unfortunate for all concerned—for clergymen to step outside their distinctive role and to assume the role of psychiatrist." Life is too short and the problems of religion and psychiatry are too large for anyone to become sufficiently expert in both fields to handle the entire problem.<sup>16</sup> Many other clergymen of wide experience have likewise appealed for continued and even increased coordination with the science of psychiatry, for the benefit of mankind.<sup>5,19,21,37,41</sup>

Psychiatrists, in their turn, have become increasingly cognizant of the personality-stabilizing capabilities of religion.<sup>13,22,23,29,32</sup> It is just as important for the psychiatrist to be religiously oriented as it is for the clergyman to be psychologically oriented. Of more than historical significance was the unanimously approved statement of 100 members of the Group for the Advancement of Psychiatry at Minneapolis on July 2, 1947.<sup>32</sup> The statement, in part, was that "The methods of psychi-

atry aim to help patients achieve health in their emotional lives so that they may live in harmony with society and with its standards. We believe that there is no conflict between psychiatry and religion. In the practice of his profession, the competent psychiatrist will therefore always be guided by this belief." There is nothing in the known structure of the psychic apparatus that a true believer and religious thinker cannot accept.<sup>45</sup> Religion cannot be measured by weighing its psychological components. Religion has a universality that attests its essentiality to human welfare.<sup>43</sup> There is a general personal psychological need for an object greater than self to which to give homage or to acknowledge superiority or indebtedness. In proportion to the degree to which psychiatry promotes harmonious adjustment to the social environment, it may be regarded as supplementing the spiritual values of life.

F. G. Ebaugh,<sup>12</sup> in his teaching of medical students and staff physicians, has always emphasized the importance of proper religious training in the development of stable and well-integrated personalities. To further the cooperation and freedom from prejudice of religion and psychiatry, he has included in his training program for psychiatric resident physicians a series of lectures by outstanding religious leaders of all denominations. Clergymen of all faiths and creeds have always felt free to inquire into the medical condition of members of their congregations who were receiving treatment at the Colorado Psychopathic Hospital. This "rubbing elbows" at the patient level is conducive to mutual understanding among ministers and psychiatrists. Likewise, practically all standardized theological schools offer one or more courses pertaining to the psychology of religion.<sup>8</sup>

This paper discusses only those patients who are ill enough to be hos-

pitalized, and leaves untouched, for the most part, that much larger group or out-patients who are only partially incapacitated by neuroses and other maladjustments. The following case histories of patients admitted to Colorado Psychopathic Hospital are presented only in sufficient detail to demonstrate the value of and the necessity for cooperation between religion and psychiatry:

Clinical Notes: Case 1. R. H. W., a 17 year old white boy, was admitted to the hospital on July 17, 1948, because of repeated suicidal gestures over a 5 month period. The history revealed that he had been almost totally deaf since the age of 3 and had suffered from deep feelings of inadequacy and frustration because of this handicap. He had spent a great deal of time day-dreaming of becoming a famous singer and pianist. He expressed extreme hostility and resentment toward his father for "always trying to keep me down, beating me with a hair brush and wishing that I were dead. He bought me bicycles and things, but he never really loved me." He had told his family that he would kill himself if they did not furnish him with the financial means for a college education as well as for vocal and piano lessons. His family could not afford this expense. His father had apparently always interpreted his son's slightest misbehavior as a serious threat against paternal authority, inflicting immediate and severe punishment. (If a child feels that he is accepted by his parents, he can usually adjust to life in spite of physical handicaps.)

Early in his treatment it was discovered that he had been an active and accepted member of a local church and had enjoyed almost a father-son relationship with the minister for many months. His minister was contacted, appraised of the boy's condition and emotional needs, and invited to visit the patient at frequent intervals. The minister adopted a non-punitive and permissive attitude with the patient and continued his previous role of the "kindly father figure." This attitude was a very valuable part of the "total push therapy" and helped the patient to plan for and accept a future consistent with his handicaps and resources.

CASE 2. A. M., a 41 year old white married woman, was admitted to the hospital on September 13, 1948, because of "alcoholism" of short duration. She immediately volunteered the information that she and her husband had had a serious quarrel and that she

desired to leave the hospital as soon as she was deemed to be in proper physical condition "so that I can talk things over with the priest." Within a few days, she was discharged from the hospital. Since that time she has been able to adjust to the realities of living, without further resort to alcohol.

This is an example of an acute emotional crisis in a fairly stable individual. Such cases often respond successfully to the psychiatric first aid administered by a psychologically-oriented clergyman.<sup>14</sup>

CASE 3. M.M., a 48 year old white married woman, was admitted to the hospital on October 10, 1947, because of bizarre activity and unprovoked "laughing spells" of several days' duration. The patient could contribute no information as to the length of her illness because of the nature of her psychosis. Her family, likewise, were of no help in this respect. Her minister said that 6 months previously she had suddenly changed from an individual who attended church services irregularly to one who spent most of her time in ardent religious activities, for no apparent reason. This information was an aid in the proper evaluation of the patient.

It is well-recognized that sudden excessive interest in religion may be a sign of beginning schizophrenia. This is of course not meant as a reflection on normal religious zeal.

CASE 4. M.A., a 43 year old white divorcee, was brought into the hospital by her minister on June 21, 1948. The minister said, "For the last few days she has been telling me that she is the meanest person who ever lived. Today she threatened to kill herself. So I brought her in."

The patient was suffering from a severe psychotic depression, which was based on the introjection of an almost unbelievable amount of hostility and resentment. Many weeks of electroshock therapy and psychotherapy were required before she was well enough to return to society.

CASE 5. R. O., a 34 year old white married woman, was admitted to the hospital on December 11, 1947, because of extreme "nervousness," depression, fear of insanity and fear that she was dying. She showed the physical findings of severe acute anxiety, namely, labored breathing, profuse perspiration, frequency of urination, dilated pupils, a very rapid pulse (158 per minute), and generalized tremors. Her condition was due to a combination of factors which included guilt

feelings over an attempted self-induced abortion, and deep-seated anger and resentment against her husband for having impregnated her.

This case is cited merely as an example of the type of patient who probably should not even be visited by a clergyman until she has "cooled off" somewhat. For, regardless of the technique that he uses, he symbolizes the ideals and conscience of humanity. The end result might be a suicidal attempt by the patient or other marked aggravation of symptomatology.

CASE 6. V. C., 40 year old single white man, was admitted to the hospital for observation on October 3, 1947. Several days prior to admission he was arrested by the local police for handling a small boy's genitalia. He had engaged in similar activities with boys since adolescence. His past history revealed the fact that a little girl had exposed herself to his view when he was six (6) years old. In some way or other his mother found out about the episode, and warned him that if he ever did it again she would cut off his sexual organ with a butcher knife. "It scared me to death when she said that, I'll never forget it." He had absolutely no interest in the opposite sex.

This type of patient can be very dangerous, especially if his aberrant compulsion is combined with alcoholism. His mother undoubtedly at least contributed to his deviant urges by her threat. This unfortunate threat was made at an age when it is normal for a small boy to develop an intense evaluation of his sexual organ and an equally intense fear of losing it.<sup>15</sup> It is probable that his first view of female genitalia intensified his fear of castration and made him more susceptible to the actual physical threat by his mother which followed shortly thereafter. For here, he saw a person without a male sexual organ. Many small boys do not know that there is a difference between the sexual organs of the male and female. The unconscious expectation of castration, if he should ever display interest in women, apparently played a role in the pathological deviation of his impulses.

Cases such as this deserve the attention of religion, psychiatry, and all other groups which are concerned with the emotional health of the individual. Similarly, it is very common for adults to threaten to "cut off" the sexual organ of a son who has been observed masturbating. A tremendous amount of emotional illness of variable degree may result from such ill-advised threats.

CASE 7. M. E., a 22 year old white married woman, was brought into the hospital by her husband on February 27, 1948, because of frequent crying spells, confusion, and a "feeling that something is going to happen to me." Examination revealed that the patient was suffering from schizophrenia.<sup>18</sup>

Her history revealed a life-long series of failures to adapt to her environment. Coupled with this was gross mishandling and misunderstanding at the hands of those responsible for her emotional health, namely, her parents, teachers, ministers and at least one physician. She was the oldest of 7 children. "When I was in the first grade another little girl told my teacher that I had cussed her (the teacher) out and the teacher told me that I needed more religion. I cried about it for days, even in school. I felt bad about it for a year." Obviously, the remark by the teacher was extremely traumatic. "I was sure a nervous child. I failed the first grade because my teacher was cross and picked on me all the time. At recess I wouldn't go back in. The teacher was always bawling me out or putting me in a corner or making me stay after school. I was mean. I had quite a few nightmares from my seventh to my fifteenth year. They were usually of falling into a pit and falling hard. Dad would hit me hard and then ask my forgiveness. I would never forgive him and had a lot of hard feelings against him. He licked me until I was 17 years old." It is apparent that no one made a serious effort to determine the causes of her anxiety, feelings of insecurity, or resentments.<sup>20</sup> Instead, she was regarded as "bad" and was subjected to the "mailed fist" type of treatment throughout her childhood and adolescence. "When I was about 11 years old I started having trouble concentrating. The theory of evolution upset and depressed me. I searched every book I could get for information on it. I was looking for arguments in favor of the Bible as I had joined the — Church when I was 12 years old. I felt a darkness coming about me. I told my teachers that I didn't believe in evolution and they gave me the dickens." Adolescent

conflicts deserve the study of educators in all fields.<sup>6,10</sup> "The first time I really lost my mind was when I was 17 years old, attending the — Theological School, which is run by the — Church. I dreamed that I was married to the Superintendent's son and then felt that I was really married to this boy for several months. I really hadn't even been out with him. I wondered why I didn't see him every night. Electricity or something must have been influencing me in some way or other then. When I told the superintendent, he bawled me out and then later took me to the doctor. The doctor told me I was merely oversexed and should get married."

The patient's description of her own acute schizophrenic episode shows that she was unacquainted with the fact that a surge of feeling for the opposite sex is normal in adolescence.<sup>10</sup> Instead, she attributed her feelings to "electricity or something." Sex instruction should be begun comparatively early in childhood in a degree suitable to the age of the child,<sup>38</sup> and should be continuous and progressive in order to insure that emotional growth keeps abreast of physical and intellectual capabilities.<sup>40</sup>

**Summary.** 1. Religious leaders and psychiatrists have become increasingly aware of what each field has to offer the other.

2. Pertinent notes from the case histories of 5 patients admitted to Colorado Psychopathic Hospital are presented and discussed to illustrate a few actual examples of how clergymen and psychiatrists have cooperated, to the benefit of the patient. The pastor and

priest deal entirely with conscious material.<sup>37</sup> The psychiatrist begins with conscious material, but, in addition, attempts to find the unconscious sources of inner conflict.<sup>1,31,33</sup>

3. One case was presented to illustrate how a parent can be a factor in a son's development of a potentially dangerous type of sexual perversion by threatening the child for showing evidence of normal sexuality. A child should be given wholesome instruction on sexual matters consistent with his age at appropriate periods. Time and space did not allow a discussion in this paper of the enormity of the problem of sexual maladjustment, which is due in part to the persistent emphasis of our culture on the "filthiness" of sex.<sup>23,35,39</sup>

4. One case was presented to illustrate how an individual's anxieties, feelings of insecurity and resentments were grossly misunderstood and mishandled by all those responsible for her guidance to emotional maturity.

5. No attempt was made in this review to present an exact division of responsibility of religion and psychiatry for mental hygiene. Such an attempt would be incomplete, as there is obvious overlapping in some areas, and too little definitive research has been done on the subject. It has been well stated<sup>44</sup> that the role of the clergyman in mental hygiene is primarily in the field of prevention, rather than in the province of cure.

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## BOOK REVIEWS AND NOTICES

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**ATLAS OF BACTERIOLOGY.** By R. CRANSTON Low, M.D., F.R.C.P.E., F.R.S.E., Univ. of Edinburgh, and T. C. DODDS, F.I.M.L.T. 168 ills., 167 in color. Balt.: Williams & Wilkins, 1947. Price, \$8.50.

THE need has long existed for an atlas of this type. The usual black and white illustrations seen in textbooks of bacteriology are poor substitutes for color reproductions of microorganisms. This atlas consists almost entirely of well chosen, accurate color plates illustrating the microscopic appearance of organisms in both body secretions and in culture, as well as the appearance of tissue sections, individual colonies, and agar slants. In addition to the pathogenic bacteria, spirochetes, fungi, protozoa, and viruses are included.

The reviewer highly recommends this atlas, to both the student and the clinical pathologist.

A. R.

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**STUDIES ON THE FORMATION OF CELLULAR SUBSTANCES DURING BLOOD CELL PRODUCTION.** By BO THORELL, Karolinska Institute, Stockholm. Pp. 120; 58 ills. London: Henry Kimpton, 1947. Price, 12 shillings, net.

THIS research publication gives quantitative data on the nucleoprotein content of erythroid and myeloid cells in various stages of hematopoiesis. A full discussion of the ultraviolet absorption technique is included. It was found that nucleoprotein content parallels cell growth and decreases with differentiation. Studies were also made on blood cells in various hematological disorders.

I. Z.

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**PRIVATE ENTERPRISE OR GOVERNMENT IN MEDICINE.** By LOUIS HOPEWELL BAUER, M.D., F.A.C.P., Diplomate, American Board of Internal Medicine. Pp. 201. Springfield, Ill.: Charles C Thomas, 1947. Price, \$5.00.

By comparing the experience of European compulsory health programs, and carefully analyzing the implications of various proposed Congressional bills, the author contends that Federal encroachment into medicine will be deleterious. The substance of the several bills and the aims of the American Medical Association are also included. Although at times the analysis seems not impartial, this book lucidly summarizes both views.

G. R.

**DISEASES OF THE EAR, NOSE AND THROAT.** By WILLIAM WALLACE MORRISON, M.D., Prof. of Otolaryngology, New York Polyclinic Medical School and Hospital. Pp. 772; 359 ills. New York: Appleton-Century-Crofts, 1948. Price, \$8.50.

ORIGINALLY published under a different title this book is now reissued in a completely revised edition. Many antiquated ideas have been discarded and the modern otolaryngologic viewpoint incorporated in 44 well assembled, clearly expressed chapters. Although certain physiologic fundamentals are described, the author fails to discuss nasal pH and its relationship to nasal medication.

This book has been written entirely for the undergraduate medical student and the general practitioner. The illustrations have been drawn by the author and are of the schematic-diagrammatic type; they are largely amplified forms of chalk drawings used to illustrate lectures as visual aids to "step-by-step" instruction in class-rooms. In their proper environment the illustrations are unquestionably very effective; as represented in the 359 illustrations, many of them are inadequate and perhaps confusing substitutes for more polished art-work. Precisely because the text is directed to non-specialists, it is difficult to understand why the author has gone to such great lengths to illustrate the technic of radical mastoidectomy; radiography in the diagnosis of paranasal sinus disease; technic of the intranasal exenteration of the ethmoid cells; technic of the various intranasal and external sinus operations; and the technic of laryngofissure and laryngectomy. Especially ineffective are the mirror views of acute simple laryngitis, acute subglottic laryngitis, acute membranous laryngitis in diphtheria, atrophic laryngitis, contact ulcer and leukokeratosis of the larynx—to name an important few.

Despite some of its pictorial limitations, the revised work is a welcome contribution to the American otolaryngologic literature.

N. F.

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**THE EPITHELIA OF WOMAN'S REPRODUCTIVE ORGANS.** By GEORGE N. PAPANICOLAOU, M.D., HERBERT F. TRAUT, M.D., and ANDREW A. MARCIETTI, M.D. Pp. 53; 22 ills. New York: The Commonwealth Fund, 1948. Price, \$10.00.



THIS book presents a comprehensive study of the epithelial structures of the normal human female genital tract. Emphasis is upon cytology, in keeping with the increasing importance of cytologic methods of study, particularly of the female genital system, which has stemmed from the senior author's own work. The cytological details of the epithelia of the various organs constituting the system are carefully correlated with one another and with the periodic changes attending the menstrual cycle. Physiologic aspects are not neglected. A comprehensive chart summarizes this functional and cytologic correlation. Much of the story is told by abundant illustrations, which include both photomicrographs and drawings. All except 1 of the 22 plates are in color and all are of excellent quality. So important to the text are the illustrations that it would be very helpful if they were scattered through the text at appropriate intervals instead of being collected in the back of the book. It is disappointing to find drawings used, in one or two instances, to illustrate the high magnification detail of low power photomicrographs.

These points are, however, but trivial criticisms of a carefully presented study that should be very instructive and useful to the gynecologist and to the pathologist who is concerned with the study of gynecologic problems.

R. H.

**ATLAS OF PLASTIC SURGERY.** By MORTON I. BEISON, M.D., formerly Director, Department of Plastic and Reconstructive Surgery, Downtown Hospital and Pan-American Clinic, New York. Pp. 304; illustrated. New York. Grune & Stratton, 1918. Price, \$15.00.

THIS book, unique in its field, is comparable to Cutler and Zollinger's *Atlas of Surgical Operations*. It is timely, simple in its presentation, and so extensively and excellently illustrated that no detail of technique escapes the reader. Although useful to experienced plastic surgeons, its chief value will lie in its aid to the embryonic plastic surgeon. The small but well-chosen bibliography (101 references) in a publication of this magnitude implies that the material is direct, brief and free of controversy. The emphasis on maxillo-facial surgery (30% of its 287 pages alone is devoted to corrective rhinoplasty and related operations) and the limitation of coverage on surgery of fresh injuries, burns and the extremities do not suit it for the armamentarium of the general surgeon. The numerous general surgeons. The experience in the performance provided a rich background on this subject, in

which he amply demonstrates his ability. He elucidates the problem concerning the relation of the deviated nasal septum and external rhinoplasty and describes examples of numerous types of deformities and their repair. The prediction is unhesitatingly made that this volume will be well received. I. R.

**PSYCHIATRY FOR THE PEDIATRICIAN.** By HALE F. SHIRLEY, M.D., Assoc. Prof. of Pediatrics and Psychiatry, Stanford Univ. School of Medicine. Pp. 442. New York: Commonwealth Fund, 1948. Price, \$4.50.

THE title indicates a difficult job. Dr. Shirley begins with a typical day in the life of an intern in a busy out-patient clinic, goes on through habit training, brain defects, intelligence testing, emotional and sexual development, environmental factor to the wide problem of mental health in a changing world. In covering a great deal of territory for the pediatrician's benefit there are a few things which a psychiatrist would say were wrong (some of the emphasis in the treatment of enuresis, for example) and much which the psychiatrist would say was superficial. But the bibliographies at the end of each chapter are excellent and can be used for further reading and the author covers much that is not attempted in the child guidance clinics. This book is clear and valuable for those to whom it is addressed. E. B.

**IDENTIFICATION OF TUMORS.** By N. CHANDLER FOOT, M.D., Prof. of Surgical Pathology, Cornell Univ. Medical College. Pp. 397; 241 ills. Phila.: J. B. Lippincott, 1918. Price, \$6.00.

THIS is essentially a handbook for the gross and microscopic diagnosis of human tumors. Each neoplasm is considered from the standpoint of source, site, gross appearance, microscopic appearance, age and sex of patient, and signs and symptoms produced. A convenient 35 page "tabular locator" subdivides tumors according to distribution and offers a short differential diagnosis on the basis of microscopic appearance. Included in the text are sections on eye and brain tumors. Differential staining reactions are mentioned where they may be useful. The section on the lymphoid tissue presents the usual confused picture of this field and splits from the unknown a few more sub-types, such as the monocytic, pleomorphic and anastomotic type of reticulothelial sarcoma. The illustrations, an important element in a handbook of this sort, are numerous but many are not well enough reproduced to be helpful in guiding to the identification of given tumors. I. Z.

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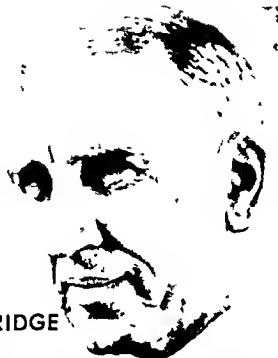
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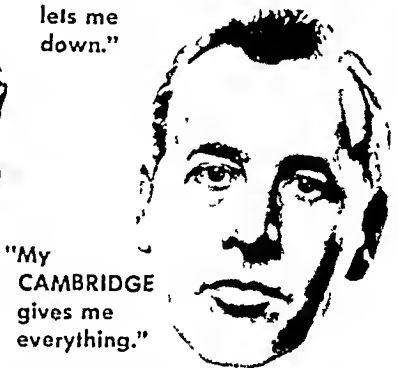
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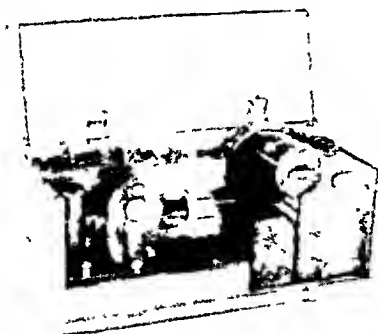


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## NEW BOOKS

*Nursing for the Future.* By ESTHER LUCILE BROWN, Ph.D. Pp. 198. New York: Russell Sage Foundation, 1948. Price, \$2.00.

*Woman's Medical Problems.* By MAXINE DAVIS. Pp. 242. New York: McGraw-Hill, 1948. Price, \$3.00.

*Pathology.* Edited by W. A. D. ANDERSON, M.A., M.D., F.A.C.P., Professor of Pathology and Bacteriology, Marquette Univ. School of Medicine. Pp. 1453; 1183 ills, 10 color plates. St. Louis: C. V. Mosby, 1948. Price, \$15.00.

*Man-Made Plague.* By WILLIAM G. NIEDERLAND, M.D., Formerly Professor of Medical Psychology and Philosophy, University of Tampa. Pp. 304. New York: Renbayle House, 1948. Price \$3.50.

*Die Organisation des Vegetativen Nervensystems.* By W. R. HESS, Prof. der Physiologie, Univ. Zürich. Pp. 226; 80 ills. Basel: Benno Schwabe; New York: Grune & Stratton, 1948. Price, \$5.60.

*The Rh' Blood Groups and Their Clinical Effects.* By P. L. MOLLISON, A. E. MOURANT, and R. R. RACE. Medical Research Council, Memorandum 19. Pp. 74. London: His Majesty's Stationery Office, 1948. Price, 1s. 6d. net.

*Annual Review of Biochemistry.* Vol. XVII. Edited by J. MURRAY LUCK, HUBERT S. LORING, and GORDON MACKINNEY. Pp. 801. Stanford, Cal.: Annual Reviews, Inc., 1948. Price, \$6.00.

THIS latest volume of a valuable series maintains the purpose and high standards set by the earlier volumes. Twenty-seven separate topics have been contributed by experts in their respective fields.

Besides such usual subjects as "Biological Oxidations and Reductions", "Carbohydrate Metabolism", "Lipid Metabolism", and "The Vitamins", the present volume contains good reviews on less frequently treated phases such as Non-oxidative Enzymes (J. B. Sumner), Chemistry of the Immunopolysaccharides (W. N. Haworth and M. Stacey), X-ray Crystallographic Studies (D. Crowfoot), Photosynthesis (E. C. Wassink), and Bacterial Metabolism (I. C. Gunsalus). Of perhaps more pertinent clinical interest are reviews on The Metabolism of Drugs and Toxic Substances (O. Bodansky), Clinical Aspects of Vitamins (T. D. Spies), The Biochemistry of Carcinogenesis (H.

P. Rusch and G. A. LePage), and The Chemistry of Penicillin (E. Chain).

D. D.

*Edinburgh Post-Graduate Lectures in Medicine.* Vol. IV Edited by the HONYMAN GILLESPIE COMMITTEE. Pp. 579. Edinburgh: Oliver & Boyd, Ltd., 1948. Price, 18s. net.

"THE lectures which comprise this volume have been delivered and published under a grant received by the Executive Committee of the Edinburgh Post-Graduate Courses. . . . The present series of lectures, given during the later stages of the war and immediately after it, deal largely with the wartime experiences and activities of the lecturers."

*Pediatrics and the Emotional Needs of the Child.* Edited by HELEN L. WITMER. Pp. 180; 16 ills. New York: The Commonwealth Fund, 1948. Price, \$1.50.

THIS book contains the opinions of pediatricians, psychiatrists, and social workers who had been assembled by the Commonwealth Fund to clarify the position and responsibilities of the pediatrician in the treatment of the "child as a whole". The discussion topics include the following: emotional growth and development of the child; mental health and the pediatrician; programs and problems in the teaching of pediatrics and mental health; integrative efforts of the pediatrician, child psychiatrist and social worker.

G. R.

*Advances in Protein Chemistry.* Vol. IV. Edited by M. L. ANSON, Continental Foods, Hoboken, and JOHN T. EDSALL. Harvard Medical School. Pp. 575; 13 ills. New York: Academic Press, 1948. Price, \$8.50.

THIS 4th annual volume continues the fine record of earlier years by presenting critical reviews of selected subjects in the chemistry of proteins and amino acids. The current topics reviewed and their authors are: Protein Gels, J. D. Ferry; The Interaction of Proteins and Synthetic Detergents, F. W. Putnam; Proteins of Pathogenic Bacteria, A. M. Pappenheimer, Jr.; The Plasma Proteins in Disease, A. B. Gutman; Preparative Electrophoresis and Ionophoresis, H. Svenson; Stereochemistry of Amino Acids, A. Neuburger; X-ray Studies of Amino Acids and Peptides, R. B. Corey; and Heme Proteins, J. Wyman, Jr.

Investigators in many fields will find something of interest and value in these reviews.

H. V.

## NEW EDITIONS

**DISEASES OF THE SKIN.** By OLIVER S. ORMSBY, M.D., Rush Prof. of Dermatology Emeritus, Univ. of Illinois, and HAMILTON MONTGOMERY, M.D., M.S., Ass't Prof. of Dermatology and Syphilology, Mayo Foundation, Univ. of Minnesota. 7th ed. Pp. 1465; 764 ills., 18 in color. Phila.: Lea & Febiger, 1948. Price, \$18.00.

THE co-authorship begun in the 6th Edition of this text has now produced a revised volume which fulfills the highest expectations of the reader. Not only has the previous high quality of this work been continued, but various improvements have been achieved. Without materially increasing the size (by 100 pages) the 7th Edition contains more than 100 new black and white illustrations and 11 new color-illustrations. A number of diseases not previously included have been added and many sections have been thoroughly revised with the aid of contributing experts. Among the revised parts particularly worthy of note are Tropical Diseases, Syphilis, Chemistry and Physiology of the Skin, Peripheral Vascular Diseases, and Mycology.

Aside from minor defects in form, the reviewer has little to criticize in this book. This edition insures it the position of leader in its field.

H. B.

**An Index of Treatment.** Edited by SIR ROBERT HUTCHINSON, Bt., M.D., LL.D., F.R.C.P. London Hospital. Assisted by REGINALD HILTON, M.D., F.R.C.P., Wembley Hospital. 13th ed. Pp. 972; 99 figs. Balt.: Williams & Wilkins, 1948. Price, \$17.00.

**Practice of Allergy.** By WARREN T. VAUGHAN, M.D. Revised by J. HARVEY BLACK, M.D. 2d ed. Pp. 1132; 333 ills. St. Louis: C. V. Mosby, 1948. Price, \$15.00.

**A Textbook of Dietetics.** By L. S. P. DAVIDSON, M.D., Prof. of Medicine and Clinical Medicine, Univ. of Edinburgh, and IAN A. ANDERSON, M.B.E., B.Sc., Lecturer in Clinical Chemistry, Univ. of Aberdeen. 2d ed. 17. New York. Paul B. Hoeber, 1945. \$6.00.

**Text of Clinical Therapeutics.** By WINDING, M.D., Prof. of Therapeutics, Univ. School of Medicine. 712. 20 ills. Philadelphia and " " Saunders, 1945. Price,

sential for proper management of medical patients. It also includes a large number of useful tables and other information in the Appendix Sections. It should prove very useful for interns and general practitioners. H. H.

**Textbook of Embryology.** By HARVEY ERNEST JORDAN, Ph.D., Sc.D., Prof. of Anatomy, and JAMES ERNEST KINDRED, Ph.D., Prof. of Anatomy, Univ. of Virginia. 5th ed. Pp. 613; 31 ills. New York: D. Appleton-Century, 1948. Price, \$7.50.

THIS well-written text should satisfy the needs of both physician and student. The recent investigations on 7 to 11 day old human embryos are well summarized, although the hormonal control of pregnancy and menstruation is slighted. Ontogenesis is unfolded in an easily understandable manner. Each chapter summarizes pertinent experimental data and lists some common anomalies. G. R.

**Gynecological and Obstetrical Anatomy.** By S. F. V. SNOOT, M.D., M.R.C.S., Univ. of Birmingham. 2d. ed. Pp. 248; 185 ills., many in color. Balt.: Williams & Wilkins, 1948. Price, \$11.00.

THIS little handbook of Anatomy is well prepared. It is limited to one particular region, combining gross and microscopic features of that region. It is well illustrated with many drawings, some photographs and photomicrographs, and a number of color plates. The amount of color in the book undoubtedly accounts for the extraordinarily high price for so small a volume. W. W.

**Manual of Veterinary Bacteriology.** By RAYMOND A. KLEBER, D.V.M., A.M., Ph.D., and HARRY W. SCHOENING, V.M.D. 5th ed. Pp. 767; 99 ills. Balt.: Williams & Wilkins, 1948. Price, \$6.50.

THE text contains preliminary sections on bacteriologic classification, morphology, and methods, followed by brief pertinent discussions of bacterial variation and infection and immunity. As the veterinary bacteriologist must often be responsible for various diagnostic laboratory procedures, sections on protozoa, filtrable viruses and rickettsiae, serology, hematology, and the preparation of veterinary biological products are also included. The original illustrations contribute greatly to the understanding of theoretical concepts. This revised edition will be welcomed not only by the veterinary profession but also by all who are interested in the pathogenesis of infectious diseases in animals. R. N.

practically every  
physician will  
require drugs  
and diet, and  
also to ex-

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### AN EPIDEMIC WAVE OF THYROTOXICOSIS IN DENMARK DURING WORLD WAR II.

BY KURT IVERSEN, M. D.,

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DURING world war II a peculiar rise in the frequency of thyrotoxicosis was observed in Denmark under the German occupation in 1941 to 1945. The rise began in 1941, all over the country, and reached its maximum in 1944. A preliminary report of this phenomenon was given in 1943 by *Meulengracht*<sup>1</sup>, who described the rise in the occurrence of thyrotoxicosis on the basis of cases admitted to his own department (Dept. B., Bispebjerg Hospital, Copenhagen). Now, in 1948, the pre-war level has again been reached. The rise was abrupt and high, of transitory or, so to speak, of "epidemic" character and its cause was so obscure, that it seemed worth analyzing in detail.

A question of particular interest for the present work is whether variations in the thyrotoxic morbidity have been seen before, especially during the war of 1914 to 1918. On this point, opinions are rather divergent. Still, a number of fairly well substantiated reports are available, showing that in Germany and Finland the incidence of thyrotoxicosis decreased considerably during the war of 1914-1918 and in the first years thereafter. Further, a rise in the frequency of thyrotoxicosis like

the one observed here in Denmark has been recorded only once before, namely: in Olmstead County, Minnesota, during the years 1924 to 1927. This "epidemic" rise has been described by *Plummer*<sup>2</sup> who states, however, that the data on which the assumption of the rise is based are somewhat defective. Thus he had no chance of ascertaining how large a percentage of the thyrotoxic patients in the Northwest and Great Lakes' region were admitted to the Mayo Clinic. On the basis of the available data Plummer would not venture to say anything about the cause of the "epidemic". After all, to me it seems more reasonable to assume that the phenomenon in question is a result of extraordinary conditions in connection with the Plummer treatment of thyrotoxicosis with iodine, which started just some years before, and thus the rise is not to be taken as a real increase in the morbidity, but rather attributable to a change in the general hospitalization of patients.

The Danish "Epidemic". In order to get an idea about the frequency of thyrotoxicosis in Denmark through a number of years, I have gone through the annual reports from all the hos-

pitals in this country within the period of 1931 to 1945. For several reasons, however, the numerical data obtained in this way are inaccurate, giving by no means the absolute occurrence of thyrotoxicosis in Denmark.

For one thing, it has to be realized that hardly all cases of this kind are hospitalized. Further, in making use of the annual reports from the hospitals it is not practicable to rule out all readmissions; besides, the same patient may be registered twice in the same annual

report, under the medical as well as surgical departments.

In Fig. 1 all the hospitalized cases of thyrotoxicosis in Denmark, *according to the annual reports*, are recorded graphically. From this it is evident that since 1931 there was a gradual and continuous rise in the frequency of thyrotoxicosis until 1941, when a sudden rise set in that continued also in the following 2 years. Thus in 1943 the number of cases was 3 to 4 times higher than in the years before the

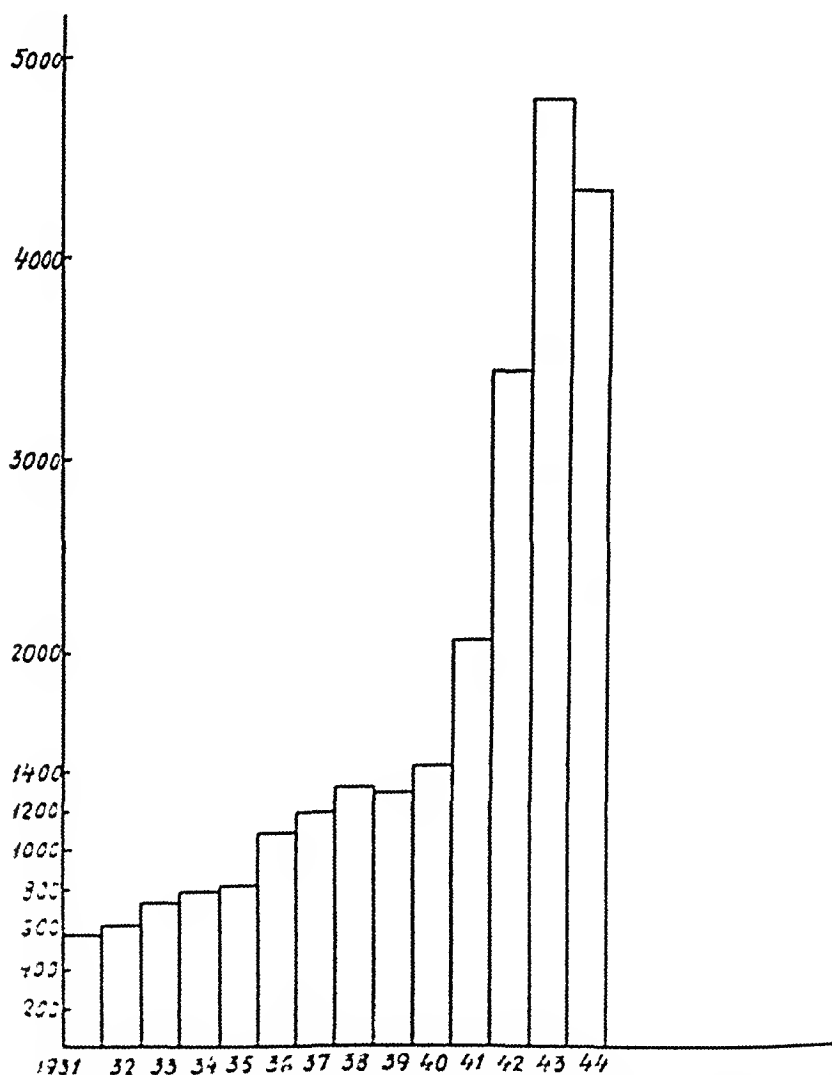


Fig. 1. All hospitalized cases of thyrotoxicosis in Denmark in the period of 1931-44, according to the annual reports from the hospitals.

war. The rise had culminated in 1944, when the incidence commenced to fall, and this fall continued in 1945.

A detailed analysis showed that the sudden rise in thyrotoxicosis in 1942 was distributed equally over all the counties of the country. It commenced at the same time all over the country and was of almost the same magnitude in the various counties.

For reasons already mentioned the annual reports are not serviceable for an accurate estimate of the occurrence of thyrotoxicosis. This requires an individual registration of each case so as to exclude readmissions and relapses. Besides, this is the only way in which

all dubious cases may be ruled out. In order to keep this task within reasonable limits I have chosen to investigate the occurrence of thyrotoxicosis within the municipality of Copenhagen. The rise in the incidence of the disease has been just as pronounced here as in the entire country and the material may be said to be representative for such investigation.

**Material.** The present material comprises *all newly-diagnosed hospitalized cases of thyrotoxicosis residing in the municipality of Copenhagen within the period of 1938 to 1947.*

No absolutely accurate figure for the occurrence of the disease in the popu-

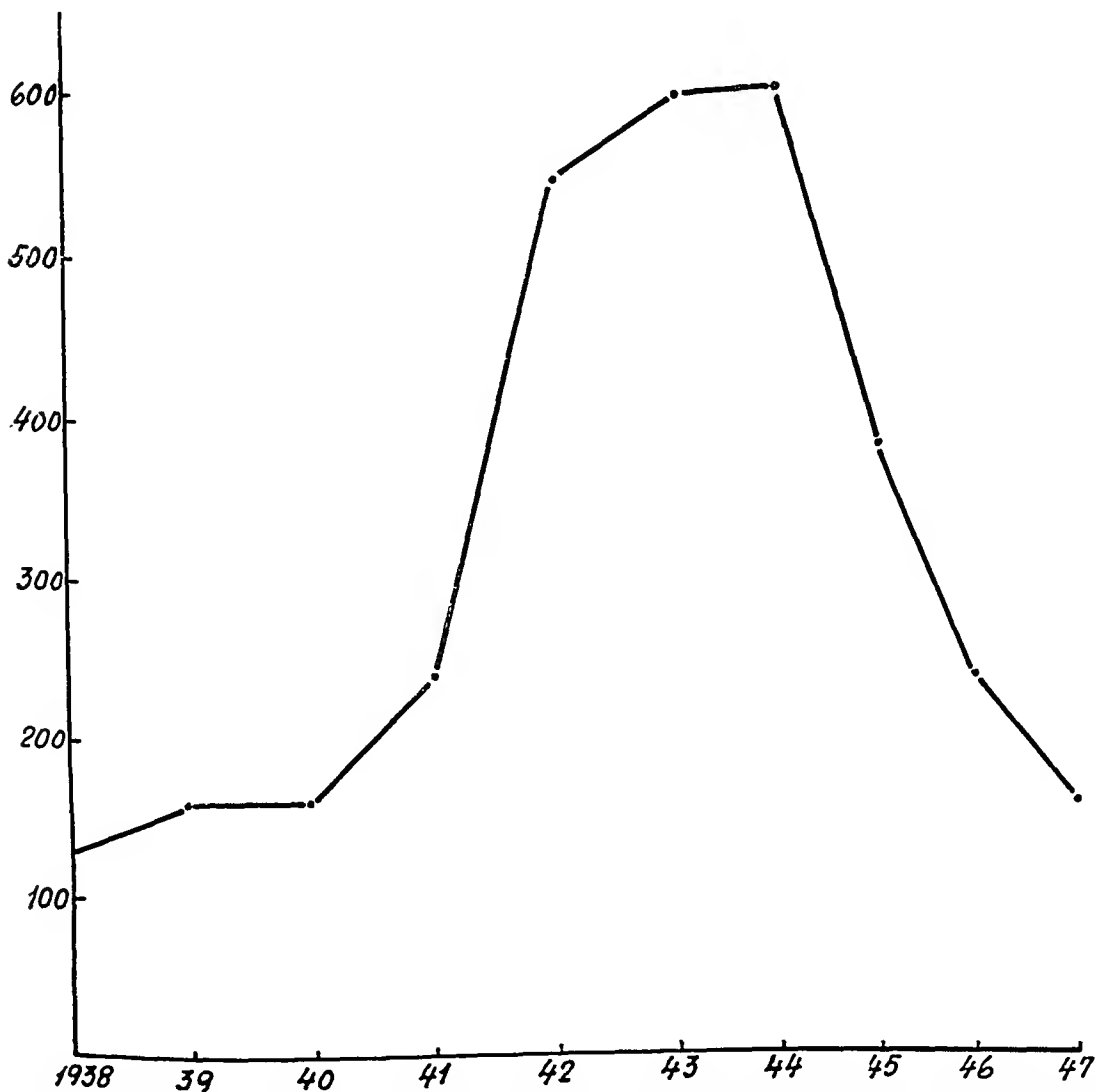


FIG. 2.—Variations in the number of first-diagnosed cases of thyrotoxicosis residing in Copenhagen and admitted to Copenhagen hospitals in 1938–47 (in absolute figures).



lation may be obtained in this way, it is true, but I feel convinced that only an insignificant number of patients here in Copenhagen have not been hospitalized at some juncture of their illness. This has further been confirmed privately by several practising physicians in Copenhagen.

TABLE 1.—SHIFT IN THE MORBIDITY OF THYROTOXICOSIS FOR THE CITY OF COPENHAGEN IN 1938 TO 1947

	No. of cases	No of inhabitants	No of cases in %
1938	129	687625	0,19
1939	159	691995	0,23
1940	160	700465	0,23
1941	240	702424	0,34
1942	546	711224	0,77
1943	598	714589	0,84
1944	591	724071	0,83
1945	379	731707	0,52
1946	235	753010	0,31
1947	157	759114	0,21

The material includes a total of 3194 cases. The average incidence of thyrotoxicosis in Copenhagen in this period is found to have been 0,44—pro mille.

In Table 1 the cases are recorded for each year together with the census for Copenhagen. In 1938 the disease occurred in 0,19% of the population, and in the following 4 to 5 years it increased so markedly that in 1943 it occurred in 0,84% of the inhabitants of Copenhagen.

In Fig. 2 this rise in the frequency is presented graphically. From this it will be noticed that the rise from 1938 to 1940 is fairly gradual, while it becomes more marked in 1941, and then in 1942 it is quite abrupt and keeps at the high level for the following 2 years. In 1944 this rise has culminated, and as early as 1945 there is a rather considerable fall in the number of cases. In 1947 the pre-war level is reached again.

From Fig. 1, which is plotted on the basis of the annual reports from all the hospitals in the country, it will be seen that the gradual rise from 1938 to 1940 practically is to be looked

upon as a continuation of the steady increase since 1931. The cause of this gradual rise in this period seems most likely to be due to greater interest in the disease and a more ready recognition of it.

As for the sudden rise in 1942, it is hardly conceivable that it might be a simple continuation of a preceding gradual rise. It is directly suggestive of some extraordinary underlying conditions.

Before discussing the cause of this peculiar rise, we first have to realize that it is due to a real increase in the morbidity and not to some irrelevant factors. And it may be at once said that neither increase in the population nor any change in the tendency to hospitalization of the patients may give any adequate explanation of the phenomenon.

It also seems improbable that improved diagnosis might bring about such a sudden rise in the frequency of the disease. As already mentioned, the increase is distributed evenly all over the country. In other words, if improved diagnosis were the cause of the rise, it would mean that all physicians throughout the country in 1942 suddenly had acquired a much greater diagnostic capacity as far as the recognition of thyrotoxicosis is concerned. It would hardly be reasonable to assume this, particularly as the disease on the whole had become more severe. Moreover, the decreased frequency of thyrotoxicosis in 1945 most decidedly goes against such a possibility. Besides, if improved diagnosis really played any rôle here, we would expect that the practising physicians now referred more patients to the hospitals with a correct diagnosis than before. But, on going through the admitting diagnoses, year by year, no particular change is found in this respect. Conceivably the rise might have been due to increasing



# IVERSEN: EPIDEMIC WAVE OF THYROTOXICOSIS

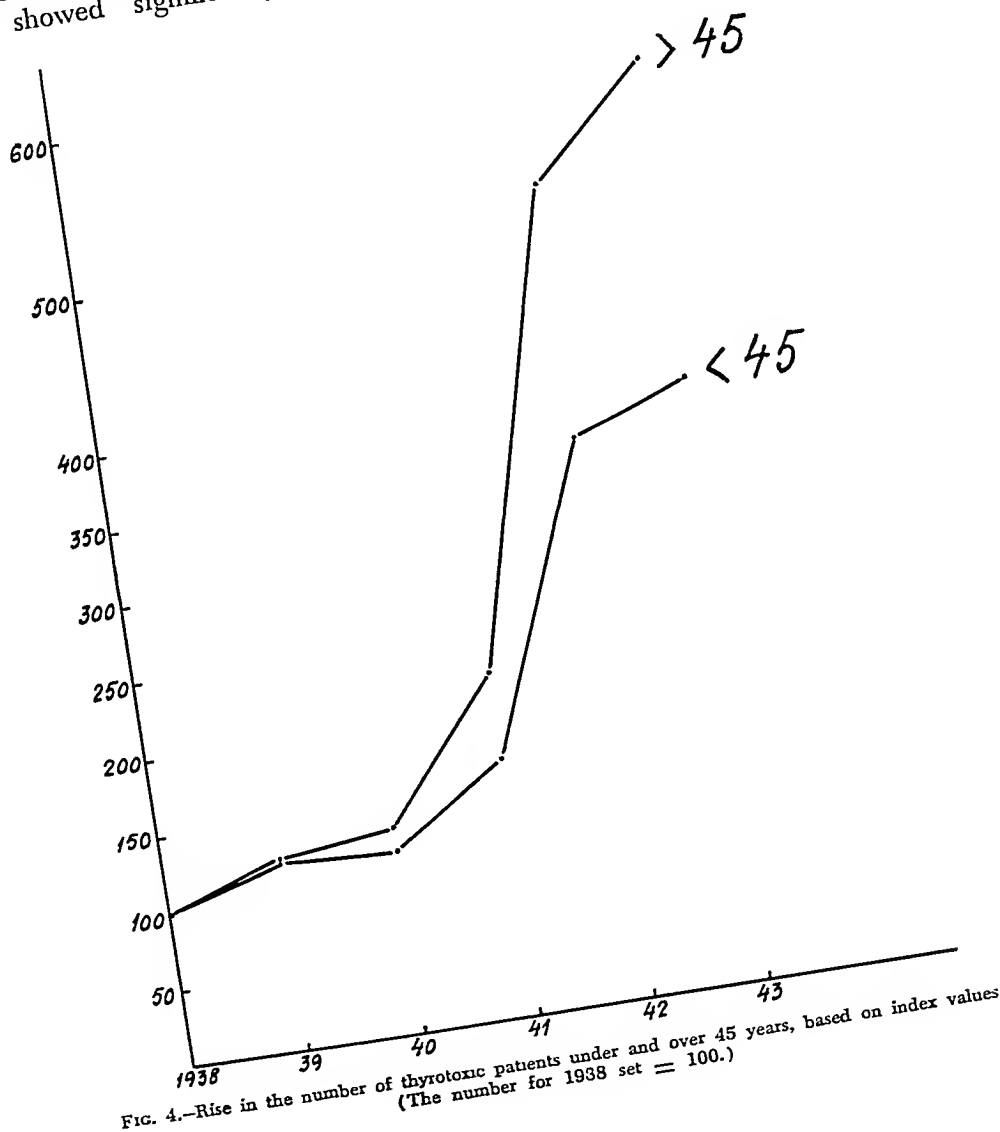
cases of new-diagnosed thyrotoxicosis, shows that *thyrotoxicosis in Denmark now appears in a more oligosymptomatic form than previously.*

It is especially the objective symptoms, however, that show the more distinct differences between the 2 groups. Thus, pronounced enlargement of the thyroid, exophthalmus and tachycardia occurred less frequently among the cases during the rise. Further, the determinations of the metabolism showed significantly higher

values for the cases during the rise and correspondingly these patients also had greater loss in weight.

It is reasonable to assume that this change in the symptomatology primarily is attributable to a greater interest taken more recently in the forms of thyrotoxicosis and thus also to a better recognition of the variegated clinical manifestations of thyrotoxicosis.

The next question is whether these "masked" or oligosymptomatic cases of thyrotoxicosis seen during the rise of



the disease may have increased to such an extent that the addition of these cases might explain the general rise in the frequency of thyrotoxicosis here in Denmark.

It proved impracticable, however, to obtain an accurate numerical expression for these cases through a retrospective investigation like this one. For it may always be questionable whether in a given case the lesion correctly has been looked upon as "masked", or whether its "masking" might not rather be due to failing diagnostic ability of the examiner. In material like the present, collected from many clinics, such a selection of masked cases could not avoid being rather arbitrary, on which account I had to give up my original plan to separate all masked cases of thyrotoxicosis in order to see whether they had increased to such an extent that the addition of these cases might explain the general rise in the frequency of thyrotoxicosis.

If improved diagnosis had played any rôle in the rise in frequency, we would expect the rise to involve exclusively—or at any rate chiefly—the older patients, as the symptoms are relatively more scanty in the higher age-classes. In Fig. 4 we see the rise in frequency for patients over 45 years compared with the rise for patients under 45. The curves here are plotted on the basis of index values, the values for 1938 set =100. The rise is found to be greater for patients over 45 years: 6 times their initial number. But the rise is also quite considerable for patients under 45 years, their number being quadrupled. In other words, this means that even the younger thyrotoxic patients—with nearly the same form of clinical manifestation of their illness—have increased considerably in number during these years.

To me these findings seem to indicate that the rise in the frequency of

*thyrotoxicosis in Denmark must chiefly be due to a real increase in morbidity even though improved diagnosis possibly may explain a part of it.*

Variations in the Frequency of Thyrotoxicosis in Countries Other than Denmark during World War II. In an investigation like the present it is of great interest to establish whether a sudden rise in the occurrence of thyrotoxicosis similar to the one observed in Denmark during the last war may have taken place at some point of time in other countries. On going through the *mortality statistics* from various countries (Norway, Sweden, Great Britain, Canada, United States, New Zealand and Holland), covering the last 40 years, it is found that since 1910 there has been a gradual, though rather considerable, rise in the thyrotoxicosis mortality. But a sudden or abrupt rise like that just observed in Denmark has not been seen before.

More recent reports from other countries indicate that *during world war II there was a distinct decrease in the frequency of thyrotoxicosis in Holland (Schweitzer<sup>6</sup>) and Belgium (Bastenie<sup>1</sup>)*. The respective authors have been most inclined to associate this fact with the general malnutrition of the Dutch and Belgian population.

In Norway, during the beginning of the German occupation, in 1941 there was a distinct rise in the frequency of thyrotoxicosis, but already, in the following year, simultaneously with the nutritional crisis, there was a noticeable decrease in the incidence of the disease that became more accentuated in the following years (Grelland<sup>2</sup>).

Through private questionnaires to a number of thyroid investigators in Europe and America, supplementary information has been obtained about the thyrotoxicosis morbidity during the war. From this it is evident that no variations in the frequency of thyro-

toxicosis was observed in Sweden, Finland, Great Britain, Switzerland, United States or Argentina. In Paris a considerable rise in the frequency of the disease also seems to have been observed, according to Alison (personal communication), but it seems to have been a localized phenomenon and not fully established.

So, while during the war and the German occupation the frequency of thyrotoxicosis rose considerably in Denmark, there was a marked fall in the incidence of the disease in Holland and Belgium, and in Norway there was a minor rise in the first year of occupation, followed by a distinct fall.

As a matter of fact, we might say that in the countries during the war a human experiment was taking place on a very large scale.

Possible causes of the temporary rise in frequency of thyrotoxicosis. One factor common to the 4 countries was the hard psychic strain to which the population was submitted; and yet the frequency of the disease differed in these countries. While in Denmark the diet in general was adequate qualitatively as well as quantitatively throughout the war, there was a considerable degree of malnutrition in the other countries, and in Norway this did not become particularly pronounced till 1942 and 1943 when the frequency of the disease fell off markedly.

At first glance these findings may be taken to indicate that psychic strain has not played any particular rôle, whereas the nutritional conditions may be assumed to have played a considerable part in the difference in the frequency of thyrotoxicosis in the countries concerned.

It must be said to be most dubious whether a psychic trauma might bring about or elicit a state of thyrotoxicosis. In the writer's material, positive data on previous psychic trauma were avail-

able only in 5% of the cases; and only in 2/5 of these patients was the interval between the psychic trauma and the first manifestation of the disease less than 3 months. This suggests that a psychic trauma cannot play any great rôle in the etiology of thyrotoxicosis on the whole.

Naturally it would be of particular interest to clear up the question whether the rise in the frequency of thyrotoxicosis in Denmark in recent years possibly might have been due to the heavy psychic strain to which the Danish population was exposed under the German occupation.

As to this point, it may be said that the psychic strain from the German occupation asserted itself more forcibly in 1944 and 1945, when the German terrorism with "clearing murder", etc., became more atrocious than before, whereas the rise in thyrotoxic morbid-ity had already commenced in 1941.

No evidence is found that would permit us to assign any particular etiological rôle to any known infectious diseases as far as the development of thyrotoxicosis is concerned. Nor has any evidence been found in support of the assumption that thyrotoxic patients would be more liable than other persons to catarrhal infections of the air passages. But it must be admitted that the demonstrated curve (Fig. 2) of the temporary rise in the frequency of thyrotoxicosis in Denmark has some resemblance to a typical epidemic curve.

Previously some experimental studies have been published, showing that exposure to cold gives rise to certain histological changes in the thyroid, indicating hyperactivity of the gland. These changes greatly resemble the picture encountered after administration of thyrotropic hormone.

In this connection attention may be called to the fact that 3 extraordinarily cold winters occurred immediately be-

fore and simultaneous with the rise in the frequency of thyrotoxicosis in Denmark. The same appears to have applied also to the wave of the disease in Minnesota in the years of 1924 to 1926 according to the annual meteorological reports. But, whether these extraordinary climatic conditions may have been connected with the rise in thyrotoxicosis cannot be decided with certainty.

The idea that the rise in the frequency of thyrotoxicosis in Denmark during the war may have been associated with *certain changes in the nutrition*, may be said to seem rather obvious. A fairly thorough analysis of the dietary conditions during this period, however, shows that only relatively slight changes have taken place. Thus, for instance, the caloric consumption was lowered from 3071 to 2687 calories per individual from 1939 to 1945. There has been a minor increase in the protein consumption, while the consumption of fat and carbohydrate has been decreasing. The "protective food" content of the diet has rather been increasing. An analy-

sis of the diet of this sort cannot give any explanation of the cause of the peculiar rise in the frequency of thyrotoxicosis in these years.

Perhaps changes in the content of some antithyroid factors of the diet may give a plausible explanation as to the origin of the "epidemic wave" of thyrotoxicosis in Denmark during the war, even though nothing definite can yet be said about it. For further details concerning this discussion, the reader may be referred to a monograph by the writer<sup>3</sup>.

Summary. A description and analysis have been given of a peculiar and temporary rise in the frequency of thyrotoxicosis in Denmark during World War II. The rise set in suddenly in 1941 and reached its peak in 1944. In 1947 the pre-war level was again reached. It is shown that the rise in the frequency of the disease in these years must be due to a real increase in morbidity. The causes of the phenomenon has been discussed briefly, but no definite and adequate explanation of this peculiar "epidemic wave" of thyrotoxicosis may yet be offered.

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# EXPERIMENTAL STUDY OF LIFE SITUATIONS, EMOTIONS, AND THE OCCURRENCE OF ACIDOSIS IN A JUVENILE DIABETIC.

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It is known that the regulation of diabetes mellitus becomes more difficult when the patient is under stress from infection or trauma, or during periods of emotional conflict. "Emotional glycosuria" has been demonstrated both in man and in experimental animals.<sup>1,4,6</sup> There has been reported the occurrence of diabetes in a setting of emotional conflict, and furthermore, fluctuations in the disorder have been correlated with the emotional state in some patients.<sup>2,3,5,7,8,9</sup> In the study here reported, the relation between ketonuria, life situation, and emotional state has been investigated.

**Case Report:** The patient was a 15 year old schoolgirl who had been admitted to the New York Hospital 13 times in diabetic acidosis. Two of these episodes of acidosis had been attributed to intercurrent infection, but the remainder were unexplained. It was generally felt that they had been precipitated by the patient's wilful neglect to take insulin and to follow her diet.

The girl was the youngest of 5 children of a Roman Catholic laborer and his wife. The father was a mild and ineffectual man, while the mother was an anxious, hypochondriacal woman who was the tyrant of the family. She exhibited mixed feelings of resentment and guilt toward the patient, who was an unplanned and unwanted child 7 years younger than her next older sibling. The mother's behavior toward the girl, consisted of extremely restrictive discipline accompanied by towering rages in which she often beat her, alternating with periods of remorse and solicitude.

There was no family history of diabetes. The patient showed no abnormalities of birth or physical development, and, until the

onset of her diabetes at age 11, she had no illness except the usual childhood diseases and an appendectomy for acute appendicitis. At a very early age, however, she showed rebellious feelings toward her mother's restrictions, as well as terror at the beatings which she received. It is not clear whether or not there were any important changes in her life situation at the time of onset of her diabetes. No evidence of such a change was elicited in numerous interviews. When the diagnosis of diabetes was made the mother was afraid of its implications, and doubled her restrictions upon the child.

At the time the patient was first seen at this hospital she was sullen and rebellious, but the general impression was that she was a child of superior intelligence (I. Q. 117) who had reacted characteristically to a frightening diagnosis. Although she was obese she showed no other physical abnormalities. During the following 4 years the conflict between her and her mother increased in intensity, and she developed repeated episodes of acidosis.

She was studied by the authors at the time of her 14th admission to the hospital. She was again found to be resentful and inwardly rebellious toward her mother. She was also extremely dependent upon her mother, passive, and unable to solve her dilemmas by positive action. It appeared that the mother's capricious tyranny had reduced the patient to a state of complete helplessness. She seemed either consciously or unconsciously to provoke many of the storms which descended upon her. She admitted that she ate indiscriminately and she stated that she often stopped her insulin because she "wanted to die." She always maintained, however, that her episodes of acidosis had begun to develop *before* she quit taking her insulin. Since her history suggested that a violent altercation with her mother usually preceded the appearance of

acidosis, it was decided to investigate the possible connection between these two events.

**Detailed Study of the Occurrence of Acidosis:** The patient was asked to keep a diary in which she recorded the happenings of the day, and expressed her attitudes and feelings toward them. Every two weeks she was seen in the clinic and the events of the fortnight were reviewed, with special attention to the circumstances surrounding the development of acidosis. No change was made in her insulin dosage, which previously had been elevated to 60 units of protamine insulin and 40 units of regular insulin in separate syringes before breakfast. Likewise, her diet was prescribed to include protein 80 gm., fat 60 gm., and carbohydrate

200 gm., limited to 1660 calories, because of her obesity. Three times a day, before meals, she examined her urine for sugar and acetone, and recorded the results in her diary. A hundred days of her life as gleaned from her diary are recorded in Figs. 1-5. There is no doubt that she took her insulin during this time. Her critical mother confirms this.

During the 1st week of the observation period the girl's life was relatively calm and uneventful. On the 8th day she decided to take a part-time volunteer job at the hospital—a decision which represented an act of unprecedented boldness and independence on her part. When she persisted in her decision despite the objections of her parents, she became anxious, "shaky," and fearful. After a

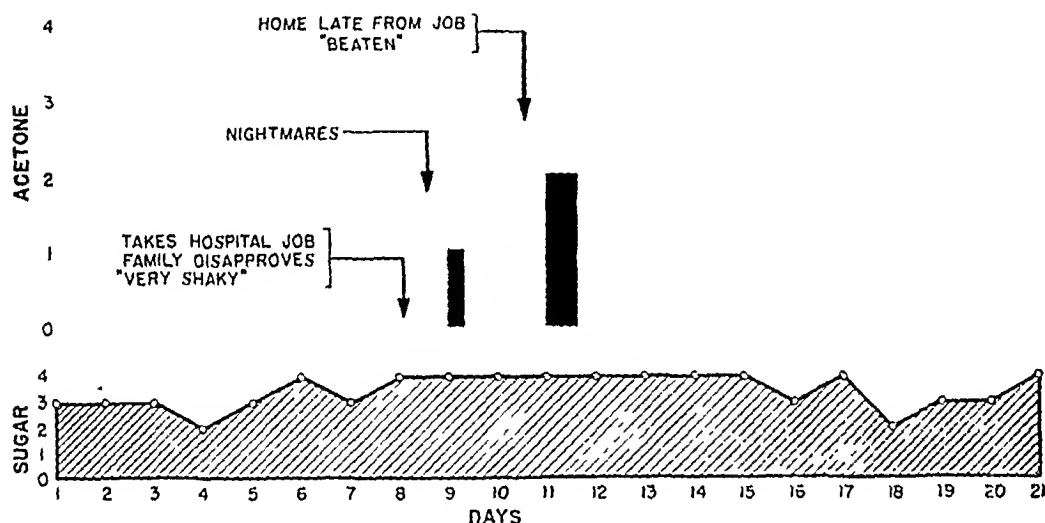


FIG. 1.—First 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions

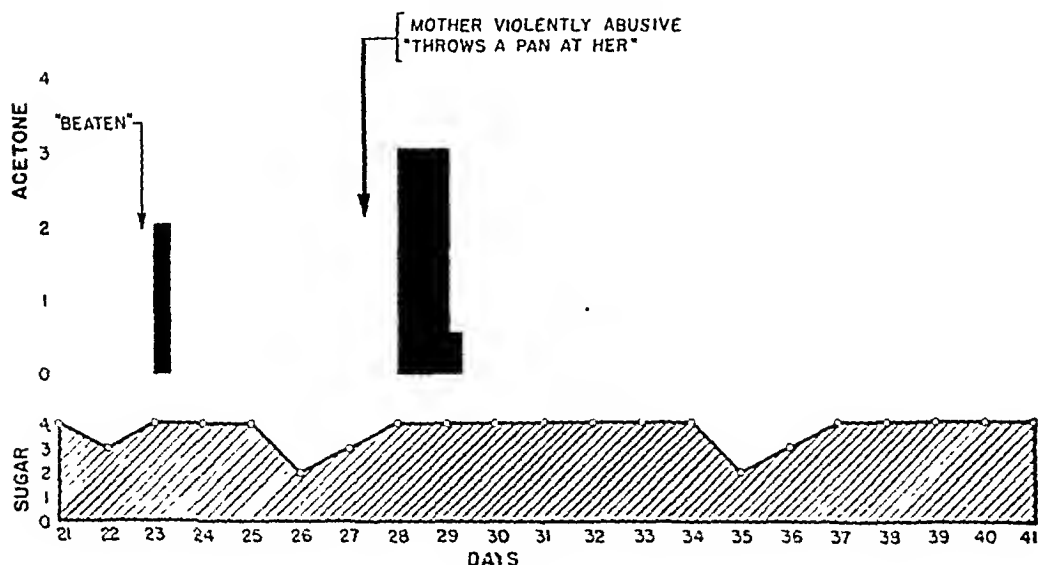


FIG. 2.—Second 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.



restless night punctuated by nightmares, she awoke on the 9th day to find acetone in her urine.

She was only partly reassured when the anticipated storm failed to materialize. On the 10th day she started work at the hospital. That night when she came home she found her mother violently angry. She was slapped with a dishrag and verbally abused for several hours. Although she became angry, she was also very much afraid. After another sleepless night she again found acetone in her urine.

Following this episode her mother was remorseful, and the patient became less apprehensive. A period of relative peace at home lasted until the 22nd day. Then an argument developed over apparently trivial matters. It was followed by a slapping. Again there was a sleepless night, and acetonuria appeared the next morning.

Several days later the mother, again feeling remorseful, bought her daughter a new dress; but shortly thereafter, on the 26th day, she once more became moody and threatening. On the 27th day the girl lost the belt

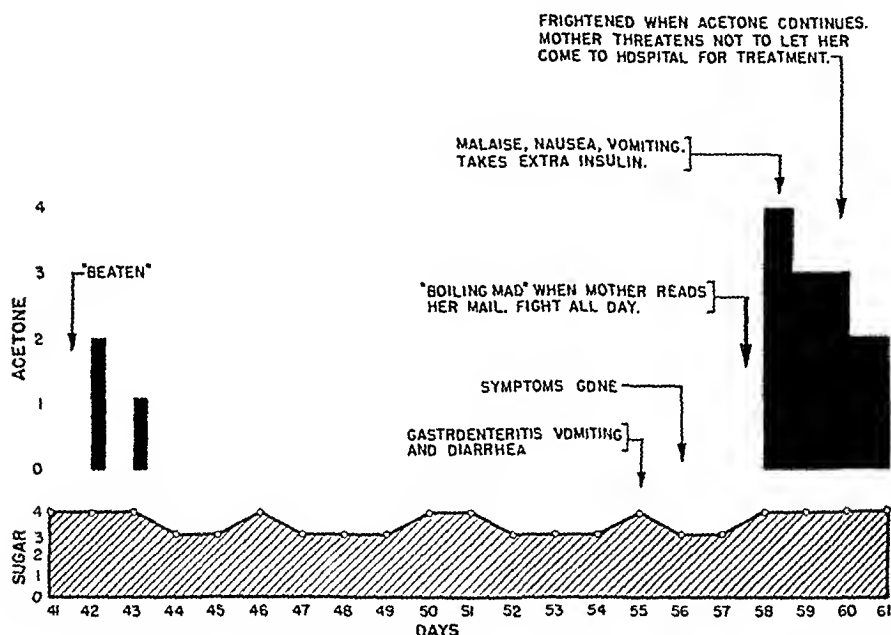


FIG. 3.—Third 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

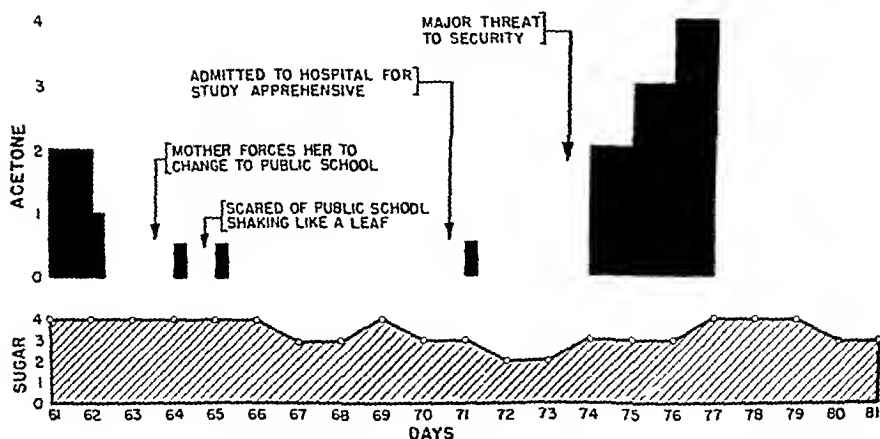


FIG. 4.—Fourth 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

to her new dress while working at the hospital. She returned home in a frightened state and received a tongue lashing that lasted several hours. During the course of it her mother threw a frying pan at her. The emotional turmoil which accompanied this episode lasted for 48 hours. Acetone appeared in the patient's urine specimen on the morning after the turmoil began. She had developed polyuria during the night, was anorexic in the morning, and then vomited several times. On several occasions during the day she took orange juice and salty broth, as well as 2 extra doses of regular insulin. Despite this, acetonuria persisted for 48 hours.

During the next week, with her mother's consent, the girl was sent to a summer camp for diabetic children. During her stay there her diabetes remained in relatively good control. However, because she was lonely she

her mother upbraided her and called her an impertinent ingrate. The girl was "as mad as I have ever been in my life," but was too terrified to make further protest. The next morning her urine contained 4 plus acetone and she began to vomit. Seeing this, her mother made her more fearful by threatening "if you get sick again, I won't take you to the hospital." Acidosis continued for 5 days and the patient again treated herself with fluids and extra insulin.

She had hardly recovered from this episode when, on the 64th day, her mother forced her to stop going to a parochial school and made her enter a public high school. She was both resentful and fearful at this move. During the first 2 days at school she was "shaking like a leaf." There was a trace of acetone in her urine at noon each day.

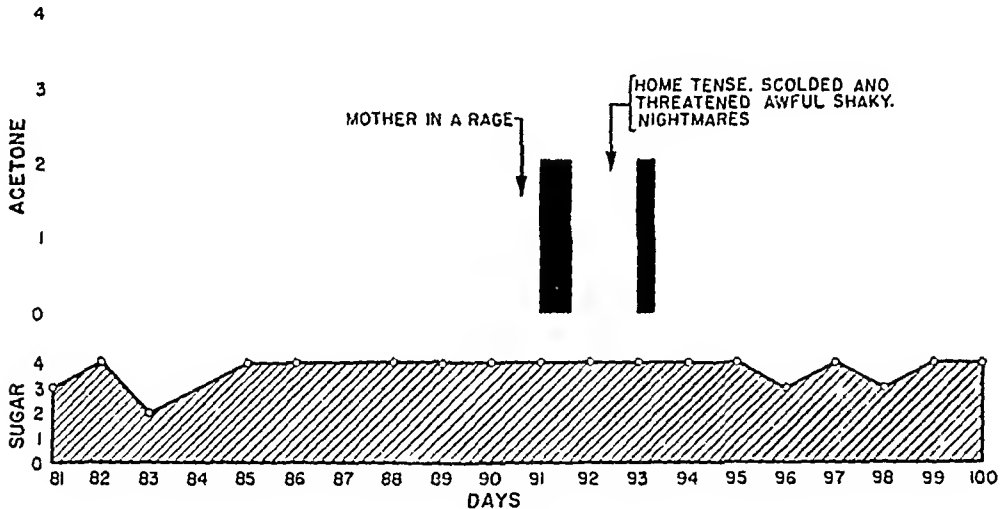


FIG. 5.—Fifth 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

came home unexpectedly on the 40th day of the observation period, upsetting her mother's plans for the ensuing week. The argument precipitated by her return home took place on the morning of the 42nd day. Acetone appeared in the noon specimen that day. It was present the following morning also.

For 2 weeks thereafter no ketonuria was reported. There were no emotional upsets during this time. On the 55th day the patient developed abdominal cramps, watery diarrhea, nausea, vomiting, and malaise, all of which lasted for about 12 hours. Her symptoms suggested that she had an infectious gastro-enteritis of moderate degree. She did not develop ketonuria.

Two days later however, after all her symptoms of gastro-enteritis had subsided, she became intensely angry upon discovering her mother reading her mail. Thereupon

On the 70th day of observation the patient was admitted to the hospital, to allow for a more detailed study of the relevance of her life situation to her bouts of acidosis. She was quite suspicious and somewhat fearful at the time of admission, and a trace of acetone was present in her urine. With reassurance she became more relaxed and soon adjusted to the ward routine. In order to regulate her activity it was arranged that she should have set chores to do under the supervision of the head nurse. She enjoyed this, feeling a sense of importance in her semi-official position. At the same time her constant association with the nurses made it possible to standardize effectively her diet. Her diet and insulin dosage were not altered. Examination at the time of admission showed no significant physical findings except obesity and a rather high tissue tur-

gor. The latter was thought to be associated with the high insulin dosage. After 3 days she was considered to be in a relatively calm, steady state. No acetone had been present in the urine since the admission specimen. Her fasting blood sugar was 200 mg. a/c at this time.

On the afternoon of the 74th day the girl's mother came to visit her physician. The two had a long and friendly chat, while the girl waited anxiously outside of the consultation room. When they left the room in serious and friendly conversation without more than a nod for her, she assumed that the worst had happened. She was allowed to gain the impression that both were angry with her. She confided later that she was convinced that her doctor (whom she regarded as her "only friend") had "gone over to Mother's side" and that the two were plotting against her. She felt angry, terrified, and helpless.

Shortly after this the nurses observed that she had a scowl on her face, and that she seemed preoccupied. She became restless, "jumpy," and complained of feeling "shaky." She had no appetite for her dinner, but forced it down. During the night she tossed restlessly in her bed and had several terrifying nightmares. About midnight she began to urinate frequently and in large quantities. The specimen contained 3-plus acetone.

When she was seen the next day she showed, in addition to restlessness and irritability, a startle reaction, acetone breath, dry tongue, rapid pulse, and cold moist palms. Her diet and activity were not altered. By evening acetone was 4 plus in all specimens, and attempts to reassure her were begun. While she was kept under observation, no other changes were made in her therapy. For 2 days fear, resentment, and ketonuria continued, subsiding slowly under reassurance.

Her subsequent course in the hospital was uneventful. By the time she left, her relation with her physician had been restored to its former state. At home she had 2 further bouts of ketonuria, each preceded and accompanied by threats to her security arising from strained relations with her mother similar to those described previously.

**Discussion.** Willms<sup>11</sup> has reported that a rise in blood ketone bodies occurs in response to exposure of relatively small areas of the body to Roentgen rays. Winkeler and Hebel<sup>12</sup> have reported a similar rise in the blood

ketone bodies after extreme physical exertion. Selye<sup>10</sup> has considered both of these phenomena as a part of the non-specific bodily reaction to stress which he calls the "alarm reaction." Inasmuch as threatening life situations which arouse emotional conflicts have been observed to initiate the alarm reaction, it may be that the ketonemia which appeared in this patient is another instance of this phenomenon.

The mechanisms by which the metabolic changes were produced is not clear. It appears that the fact that ketosis has been so readily elicited in this diabetic is in part related to her acute sensitivity to any threat which tends to disturb her relation to her mother. This relation to her mother is colored by intense and conflicting emotions at all times, even the "calmest." Her reaction to any disturbance of it includes not only ketosis, but also diuresis, restlessness, tachycardia, increased perspiration and a mood change characterized by anger, fear, and moderate depression. Part of this reaction—the tachycardia and increased perspiration, for example—appears to be mediated by the hypothalamic-sympathetic system. It seems reasonable to conjecture also that the pituitary, acting by itself and through the adrenal cortex, may play an even more important part in the reaction, especially in raising the blood sugar and increasing the severity of the diabetes. Perhaps the constant action of this later mechanism day after day may also explain why her diabetes is so severe and so resistant to treatment, and why her daily insulin requirement is so far above the 40 units required by the depancreatized human.

**Conclusion.** In an anxious, maladjusted, and severely diabetic 15 year old girl, it has been shown that stressful life situations which aroused the emotions of fear and rage were ac-

accompanied by alterations in the metabolism. One manifestation of these alterations was the appearance of ketonuria within approximately 12 hours of the onset of the stressful situation. With continuation of the stress under

experimental conditions the ketosis was observed to continue to the point of clinical acidosis. Without change in diet or additional insulin the acidosis disappeared when the subject regained confidence and security.

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# LONG TERM ANTICOAGULANT THERAPY FOR CARDIOVASCULAR DISEASES\*

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ANTICOAGULANT therapy has now been well established in the treatment of various thrombo-embolic conditions. Many authors,<sup>2,3,4,6,8,9,12,13,14</sup> including ourselves, have stressed the need for careful hospital and daily laboratory supervision. There are certain patients with recurring thrombotic and embolic tendencies who need anticoagulant therapy for long periods of time. In some instances, this may mean for the remainder of their lives. This is particularly true of patients with old rheumatic heart disease complicated by valvular damage and auricular fibrillation who release showers of emboli to the peripheral circulation from time to time. Recently, we reported in some detail such a group of patients who had been treated with anticoagulants.<sup>14</sup> Aside from the value of maintaining a state of cardiac compensation, this is the only therapy thus far suggested which reduces the incidence of embolic complications and thus favorably affects the clinical course of this type of patient.

There are other types of cases in whom it is advisable to continue anticoagulant treatment for an indefinite period. These include patients with phlebitis migrans, recurrent thrombophlebitis and certain patients with recurrent coronary thromboses and myocardial infarction in whom it is desirable to continue anticoagulant ther-

apy as a prophylactic step against further recurrences. Nichol and Fassett<sup>7</sup> have reported experiences with this type of patient.

The purpose of this report is to present experiences with long continued anticoagulant treatment and examples of difficulties which may be encountered. To subject a patient to a daily intravenous puncture to procure blood for a prothrombin test is, in general, only feasible for a few weeks while he is in the hospital. After he leaves the hospital and becomes ambulant, a daily test is too time consuming, uncomfortable and expensive. It interferes greatly with the patient's daily life. The following plan has, therefore, been adopted for the care of such cases. Each patient's idiosyncrasies to dicumarol are studied while in the hospital. His daily requirements are evaluated. After 3 or more weeks of hospitalization, if the underlying disease is under control, the dicumarol requirements fairly stable, and the patient ambulant, he is discharged to his home on a specific daily dose of the drug. Thereafter, he reports twice weekly for prothrombin tests and a prescription of the daily dose. If the blood prothrombin level shows only minor fluctuations, this time interval is extended to once weekly. Some rare patients remain very stable and under these unusual circumstances the interval may be prolonged from 10 to 14

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days. In general, however, this is not to be recommended.

Serious study of this aspect of the treatment of ambulant patients with dicumarol has been carried out by the authors during the past 2 years. Since this treatment was known to be fraught with some risk, it was obviously important that patients be disciplined to take the exact amount of dicumarol prescribed and no more, and that they appear for tests as scheduled. For this reason, only intelligent and co-operative private patients have been selected for this regime.

The Link-Shapiro modification of the Quick method has been used to estimate the prothrombin time.<sup>5,10,11</sup> With the active rabbit lung thromboplastin used in our laboratory, the value for normal controls is 14 to 16 seconds. In treatment the aim is to determine a daily dose of dicumarol which will maintain the prothrombin time at from 30 to 35 seconds. This is termed the "therapeutic level."<sup>\*</sup> Minor fluctuations outside of this range, but between 25 and 45 seconds, are not considered serious.

<sup>\*</sup> To orient those readers who are accustomed to calculate prothrombin activity in percentage of normal, the comparative figures from our laboratory are listed below. Only active thromboplastin, which is tested daily against a normal person's blood and which gives a reading of from 35 to 41 seconds with a dilution, 1 part of plasma with 8 parts of saline, is used. If the thromboplastin does not come within this range, it is discarded and a new batch tested.

%		%		Sec.
100	plasma	0	saline	15±1
50	plasma	50	saline	17±1
25	plasma	75	saline	25±2
12.5	plasma	87.5	saline	38±3
8.33	plasma	91.67	saline	53±4

We have found that there is a great difference in the dose required to maintain this level from individual to individual. C. D. (Patient 13, Table 1) has an average weekly maintenance re-

quirement of 175 mg. L. B. (Patient 1), on the other hand, requires a weekly dose of 800 mg. As will be noted in Table 1, there is no apparent correlation between body weight and the size of the dose in adults. Perhaps if all other factors which enter into this picture were equal, such a correlation would be more obvious. Age is not a factor, with rare exceptions. The average requirement in a stable patient remains fairly constant over a period of time. Patients standardized 1½ years ago usually require approximately the same amount of dicumarol today.

Some women show variations in the prothrombin time with their menses, but others apparently have no change. M. M. (Patient 8) usually requires an increase in dicumarol dosage just before and during her menses to maintain her therapeutic level. This has been observed for 16 months. During the menstrual week she needs 575 mg., during the other 3 weeks 475 mg. is usually sufficient. Studies of relationship of the estrogens to this finding are under way. In our experience, at therapeutic levels, dicumarol rarely increases menstrual flow in the absence of pathological states.

It appears probable that diet plays a rôle in the utilization of dicumarol.

CASE 13. Mrs. C. D. could not be standardized on dicumarol dosage until she was placed on a high protein diet. After she was first stabilized in the hospital and then maintained on ambulant treatment, she occasionally developed sudden, high values of her prothrombin times. On one occasion, the prothrombin time was unexpectedly found to be 109 seconds. She was given intravenous vitamin K therapy. Upon close questioning, it was found that this patient's sudden prolongations of prothrombin time were subsequent to the ingestion of large amounts of whiskey. Reducing the consumption of whiskey resulted in a more uniform test from week to week.

Two possible explanations occur: (a) that the alcoholic consumption in some way temporarily interfered with

prothrombin production in the liver, (b) that the intake of protein was significantly reduced when considerable alcohol was taken. The relation of protein intake to dicumarol utilization was called to our attention personally by Jorpes<sup>6</sup> and by Zilliacus<sup>16</sup> during their recent visits to this country.

In most patients there has been little difficulty in administering the treatment and very encouraging and successful results have been obtained. An example of such a case follows:

CASE 2. J. C., a 53 year old housewife, who developed rheumatic fever at 28 years of age, and had 5 recurrences thereafter. She developed auricular fibrillation approximately 5 years before the present hospital admission. It has been paroxysmal, with great variations in the duration of attacks. Her first recognized embolus occurred in 1944. This was cerebral and she became unconscious. She remained in bed for approximately 6 weeks and she made a complete recovery. The second embolus occurred on May 30, 1946, producing a sudden complete loss of consciousness. This probably was cerebral also. In June 1946, she had emboli to both legs. On July 7, 1946, she developed a sharp pain in the right hip and also one in the chest followed by bloody sputum which was probably secondary to a pulmonary infarction. On July 14, 1946, she had an embolus to the right leg. Anticoagulant therapy was not started at that time, but was begun on September 24, 1946. She received dicumarol while in the hospital for 1 month, since which time she has been ambulatory. She requires approximately 500 mg. of dicumarol per week. On December 16th, she began to have excessive menstrual flow which continued for approximately 10 days. Her prothrombin time ranged between 24 and 28 seconds; therefore it seems unlikely that this was responsible for her excessive flow. The dicumarol was discontinued and vitamin K, 2 doses of 64 mg. each, was given. A gynecologist believed that the excessive flow was due to menopausal changes and a dilatation and curettage was performed, followed by irradiation. She then resumed dicumarol. There have been no emboli since she first began dicumarol.

CASE 3. E. S., a 42 year old housewife, had typhoid fever at 3 years of age, scarlet fever at 4 years, and rheumatic fever at 5 years. Rheumatic heart disease was recognized during the 6th year. Chorea was diag-

nosed at 6, 10 and 12 years of age. Since the age of 33 her heart has been in a state of auricular fibrillation, and during these years she has taken digitalis daily. In 1935 she had an embolus to the left groin and also a pulmonary embolus. In 1942 she had a left cerebral embolus which produced a right hemiplegia from which she made a complete recovery. During the years of 1943 to 1944, it was estimated that she had at least 6 emboli, which were apparently small, in various locations throughout her body. In December, 1945, she developed 2 emboli, one renal and one mesenteric. In January, 1946, she developed her 13th definite embolus which was pulmonary, and in September, 1946, her 14th embolus which was also pulmonary. On November 15, 1946, she became decompensated. Two days later there occurred the 15th embolus to the right arm. This produced coldness, blanching, loss of pulsation below the elbow, and appeared to endanger the arm. On November 19th, she developed the 16th embolus which was to the left leg; on November 25th, a 17th embolus to the right lung field; and on December 3rd, her 18th to the right lower quadrant of the abdomen which produced shock, paralytic ileus and later blood in the stool. On December 3rd, she developed her 19th embolus which was to the left leg. On December 20th, she developed an embolus which was to the left forearm and produced marked generalized shock. The patient was acutely ill. Her outlook appeared extremely serious.

On the day of her 20th embolus, because of her desperate condition, she was started on anticoagulant therapy despite the blood in her stools, which was believed to be secondary to a mesenteric infarction. She received 52.5 mg. of heparin intravenously at 9:00 p. m., December 6th; 52.5 mg. at 1:00 a. m., and 50 mg. at 6:15 p. m., December 7th. She was also given 300 mg. of dicumarol on December 6th, followed by daily doses of 200 mg., and thereafter was regulated in accordance with the indications of her prothrombin times. She was continued for 1 month on this regimen while in the hospital. Her average requirement of dicumarol was 300 mg. weekly. Following the initial administration of anticoagulants, there was an immediate cessation of her embolic phenomena and a completely uneventful course. She was discharged from the hospital on January 6, 1947. She has since continued to receive anticoagulant therapy while ambulatory. She has had several episodes of echymoses of a very mild degree. Her prothrombin time has in general been kept between 25 and 35 seconds, the highest having been 44 sec-

onds. No further embolic episodes have occurred in a period of 15 months. The patient's general condition is excellent; she is able to travel and does so freely and without difficulty whenever satisfactory prothrombin studies can be arranged. By planning, it was possible for her to travel from New York to the Pacific Coast and return, having had prothrombin tests weekly at reliable laboratories en route. The trip was without untoward incident. Her heart continues in a state of compensated auricular fibrillation.

CASE 1. L. B., a 39 year old housewife, developed rheumatic fever at 4 years of age. From then until she was 12, she had multiple attacks of rheumatic fever with the development of a heart lesion. In 1941 she developed auricular fibrillation and was found to have mitral stenosis with cardiac decompensation. In February, 1946, she had a severe saddle embolus. She was then given heparin for 2 weeks. The embolus apparently divided, descending into both legs and leaving her with occlusion of the major arteries below the knees bilaterally. In 1946, between February and June, she suffered 6 embolic episodes, involving her legs and also her abdomen and brain. In September, 1946, she had an embolus to her right foot, and again one to each leg. On November 2, 1946, she developed a cerebral embolus which produced dizziness, diplopia, slurring of speech, involuntary twitching of the right arm, occipital headaches and loss of convergence of the left eye. She was admitted to The New York Hospital on November 3rd and dicumarol was started at that time. She remained in the hospital for 1 month, since which time she has been ambulatory. Her average weekly requirement of dicumarol is somewhat higher than that of most patients. She needs approximately 800 mg. per week to maintain a level between 28 and 35 seconds. She has had no further emboli and leads a rather active life.

CASE 7. Colonel R., age 57, developed phlebitis of the right leg in July, 1944, while in military service. Pulmonary emboli occurred in August. In November, 1944, the phlebitis recurred in the right leg. A femoral vein ligation was performed. In January, 1945, pulmonary emboli again developed. His inferior vena cava was ligated. In February both legs were swollen. Phlebitis was found in the left leg in March. By June, phlebitis had involved the veins of his anterior abdominal wall. He was retired from military service because of disability. He continued to have bouts of phlebitis in both his legs and arms. We saw him for the first time in May, 1946. He was hospitalized for 2 months and placed on anticoagulant therapy. He remained

free of phlebitis for 4 months, and then allowed his treatment to lapse. Phlebitis recurred in his arm. Dicumarol was resumed on what will probably be a permanent basis. He is now free of any active phlebitis. He has resumed moderate activity after nearly 3 years of invalidism.

The hazards of ambulatory treatment are well illustrated by the following case:

CASE 5. H. S., age 29, who suffers from a migratory thrombophlebitis. When maintained on proper dicumarol dosage, his phlebitis is quiescent. When his prothrombin time falls below 25 seconds, he almost invariably develops thromboses in the veins of his legs or arms. A dose which is too great for his immediate needs sends his prothrombin time soaring. He then tends to hemorrhage, usually under the skin. He has, therefore, a very narrow therapeutic zone within which to prevent thrombosis on the one hand and hemorrhage on the other. He is exceptional in this regard. In July, 1947, the chemist, who was working on this case with us and is expert at determining prothrombin times, was suddenly stricken with a coronary thrombosis himself. (He was treated with anticoagulants and constitutes Case 16 in this series). His technical assistant then substituted for him. As frequently happens with technicians who are inexperienced with this test, certain errors occurred during the first few days in the case of H. S. (Case 5). On one day when the prothrombin was reported as 24 seconds, he suddenly developed large subcutaneous ecchymoses. He was admitted immediately to the hospital where his prothrombin time was found to be 180 seconds by our research laboratory. He was given 72 mg. of synthetic vitamin K every 4 hours for 4 doses, and one 500 cc. transfusion of fresh blood. His prothrombin time fell gradually to therapeutic levels and there was no further bleeding. Seven months later he again encountered difficulty. At this time he was fairly well standardized on a daily dose of 50 mg. of dicumarol. One day his prothrombin time was found to be 33 seconds; seven days later it was 108 seconds. He was given 3 doses of synthetic vitamin K, 72 mg. each, 4 hours apart. The next day the prothrombin time had fallen to 83 seconds, the following day to 57, and 2 days later it was 21 seconds. At this level, thrombi promptly developed in the superficial veins of the right calf. In spite of these occasional difficulties, he has continued to work at a responsible job during the past year.



One cannot belittle the hazards of dicumarol therapy with this man, yet they must be weighed against the risks of his serious disease—thrombophlebitis migrans. Prothrombin times should be performed twice weekly for the proper control of this patient.

Another case illustrated further the danger of unreliable laboratory data.

CASE 6 G. G. a woman, age 25, was seen in consultation in a suburban hospital. She had recurrent thrombophlebitis involving deep pelvic and abdominal veins, and probably one renal vein. While awaiting transfer to The New York Hospital, she was given dicumarol. After 5 days, her prothrombin time was reported by the laboratory of the suburban hospital as 27 seconds. The following day, she was admitted to the New York Hospital. The prothrombin test was carried out by our research laboratory. No end point could be found. It was reported as 300 seconds plus, the longest time we record. (It is quite unlikely that this rise occurred in 24 hours). This patient was given intravenous vitamin K and 2 transfusions of fresh blood during the next 3 days. The prothrombin time gradually fell to a therapeutic range. She experienced no bleeding except for a slight oozing from the gums when she sucked on them. She was discharged later from the hospital and has remained on ambulant treatment without difficulty for the past 6 months.

M.M., age 44, Case 8, previously referred to, has also on 2 occasions inexplicably developed high prothrombin levels that required intravenous vitamin K injections.

It is now routine to give 2 doses of 72 mg. each of vitamin K intravenously at 4 hour intervals when the prothrombin time reaches 60 seconds or more. This has almost without exception been sufficient in cases with prothrombin times of less than 100 seconds.

An example of another type of difficulty is cited as follows:

CASE 4. M. S., a school teacher, 51 years of age, had rheumatic fever at the age of 23 with subsequent mitral stenosis. Beginning in 1942, she developed auricular fibrillation. In the summer of 1945, she developed a pulmonary embolus. This was followed during the next year by emboli to the right leg, the

abdomen, the left leg, and then again to the abdomen. Anticoagulant therapy was begun. She had no further emboli. She had a very difficult domestic situation to cope with and began to show emotional instability. It became doubtful that she would continue to follow explicit directions, so her anticoagulant treatment was discontinued. Seven days later, she had an embolus to the right area, blocking the brachial artery at its bifurcation.

It is likely that many of these patients should justifiably continue anticoagulant treatment for years to come, perhaps for life, or until better therapeutic means are developed. They must for the present, at least, take their required doses of dicumarol and have periodic prothrombin tests, just as a diabetic must take his insulin daily and have his urine and blood sugar determinations performed periodically.

Toxicity. The problem of overdosage has already been mentioned. The possibility of serious damage to the liver, kidney or other organs during prolonged administration of dicumarol has been carefully considered. We have found no clinical evidence of such toxicity in this group of patients. This confirms the first report of one of us<sup>15</sup> on the use of dicumarol. It agrees with the report of Nichol and Fassett<sup>7</sup> of an autopsied patient who had received dicumarol for 21 months.

Summary and Conclusions. (1) A group of 19 patients has been maintained for from 5 to 20 months (average 11 months) on dicumarol. Their prothrombin time has been checked every 7 to 14 days after having been carefully standardized at more frequent intervals during several weeks or months of hospitalization.

(2) This method requires constant vigilance on the part of the physician, and faithful cooperation from the patient. It necessitates a laboratory skilled in performing prothrombin times.

(3) No effort has been made to evaluate statistically the results of this therapy in this report. The object has been

to make available experiences with this clinical problem and to discuss the manner in which they have been met.

(4) Neither age nor weight constitutes the determining factor in the dosage requirements for this form of treatment.

(5) Diet apparently plays some part in the dicumarol requirements. An adequate protein intake helps to stabilize the requirements in some patients. Excessive alcoholic intake may affect the requirements.

(8) No discernible damage to the liver or kidneys has occurred in any patient as a result of the prolonged administration of dicumarol.

(9) No thrombo-embolic episode has occurred in these patients while their prothrombin time has been at a "therapeutic level" (prothrombin times above 30 seconds).

(10) There have been no deaths in this series despite the seriousness of the condition of many of these patients at the time of onset of the therapy.

TABLE 1.—PATIENTS RECEIVING DICUMAROL THERAPY

No.	Name	Diagnosis	Months on Dicumarol (to May 1, 1948)	Average Weekly Dose (Mg.)	Age (yrs.)	Weight (lbs.)
1.	Mrs. L. B.	Rheumatic Heart Disease Mitral Stenosis Auricular Fibrillation Multiple Emboli	18	800	39	110
2.	Mrs. J. C.	" "	20	500	53	125
3.	Mrs. E. S.	" "	17	300	42	112
4.	Mrs. M. S.	" "	9	700	51	137
5.	Mr. H. S.	Phlebitis Migrans	11	300	29	167
6.	Mrs. G. G.	" "	9	350	25	126
7.	Col. G. R.	" "	12	300	57	166
8.	Mrs. M. M.	Recurrent Phlebitis	19	500	44	133
9.	Mr. K. N.	" "	16	500	56	205
10.	Mr. A. S.	" "	9	450	44	155
11.	Mrs. J. S.	" "	12	400	31	140
12.	Mrs. E. W.	" "	12	700	48	203
13.	Mrs. C. D.	" "	12	175	40	145½
14.	Mr. H. C.	" "	8	550	52	158
15.	Mr. A. H.	Coronary Artery Thrombosis with Myocardial Infarction	9	350	47	165½
16.	Dr. M.	" " "	9	315	50	144
17.	Mrs. A. M.	" " "	5	300	49	116
18.	Mr. S. D.	" " "	5	350	52	183
19.	Mrs. C. S.	" " "	8	400	66	158

(6) Prothrombin times of more than 300 seconds have occurred without serious hemorrhage. Sixty seconds is regarded as the upper limit of the desirable and safe therapeutic range.

(7) Excessive prothrombin times have all been controlled with vitamin K in adequate doses and whole fresh blood transfusions.

(11) No serious hemorrhages have developed in any of these patients despite their having been almost constantly under dicumarol therapy.

(12) This method of therapy has enabled most of these patients to lead fairly normal social lives, and, where necessary, to support themselves and their families. They have been able to

accomplish much that had been beyond their possibilities prior to the use of dicumarol because of frequent emboli and thrombotic episodes. This statement includes those patients who have occasionally developed complica-

tions such as have been described.

(13) The further development of the ambulatory treatment of thrombo-embolic diseases with anticoagulants will greatly broaden its application and usefulness.

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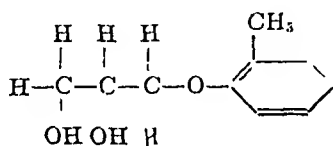
# EFFECTS OF MYANESIN UPON THE CENTRAL NERVOUS SYSTEM<sup>\*</sup>

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MYANESIN, one of a series of alpha substituted glycerol ethers was inves-



Formula of Myanesin (British Drug Houses),  
Tolserol (Squibb); 3-ortho-toloxyl-1,  
2-propanediol.

tigated by Berger and Bradley<sup>1,2,3</sup> who found that it produced in animals a profound muscular relaxation without unconsciousness. In higher doses they noted analgesia, ataxia, arousable sleep and complete paralysis. It is a local anesthetic. They thought that the chief action of the drug was upon reflex excitability of the spinal cord, because the convulsions of strychnine were effectively prevented while those from metrazol (leptazol), supposedly acting upon higher centers, were much less influenced. With large doses a peripheral curare-like effect was demonstrated in nerve-muscle preparations. Mallinson<sup>9</sup> first employed myanesin in humans to aid relaxation in general anesthesia.

The chief clinical interest in the compound stems from the observation by Stephen and Chandy<sup>11</sup> that the drug abolished the tremors and rigidity of Parkinsonism and reduced the move-

ments of choreo-athetosis at a dose which did not impair strength or consciousness. In this action the drug is unique. Electroencephalogram patterns of their cases were unaltered by the drug. From their observations they concluded that the chief site of action was upon structures lying between the cortex and the spinal cord. Schlesinger *et al.*<sup>10</sup> found, in addition, with somewhat larger doses, a depressant effect on spinal cord reflexes.

We have been investigating the effect of myanesin upon various pathological states in order to determine its sites and modes of action and to evaluate its therapeutic possibilities. We have been able to confirm several of Stephen and Chandy's observations and to add some others of interest. The usual common effects of the dose we employed consisted of a subjective sense of warmth, relaxation and slight giddiness, but not impairment of mental faculties. Two patients became faint when placed upright while under drug action. Nystagmus, slurred speech and loss of eye convergence were ordinarily observed. Normal electroencephalographic patterns were unaltered.

The tremor of Parkinsonism was abolished (in 7 cases) and choreoathetotic movements were suppressed greatly or completely (in 4 cases)

<sup>\*</sup> This study was supported in part by the Kirby-McCarthy Fund.

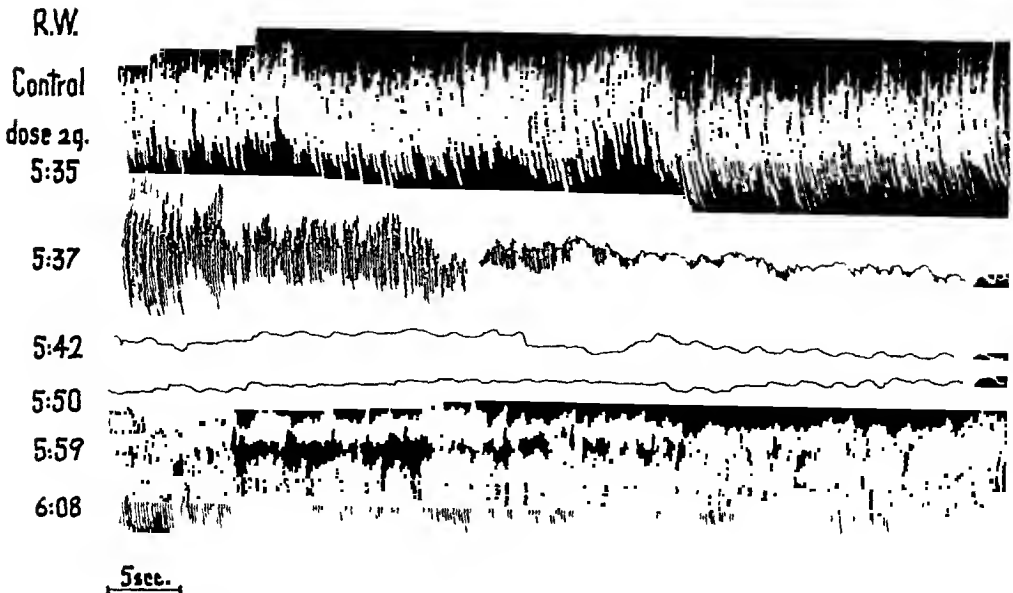


FIG. 1.—Effect of myanesin on Parkinsonian tremor. R. W. Record of tremor recorded from index finger connected by cord to muscle lever writing on smoked drum. Record continuous in each line, beginning at stated time. First line control. Second line, 2 minutes after start of infusion, shows great decrease in amplitude and frequency of tremor, which is completely (lines 3 and 4) suppressed for about 20 minutes, then gradually returns. Movement in lines 3 and 4 are due to respiration. Time 5 sec. Total dose 2 gm. myanesin.

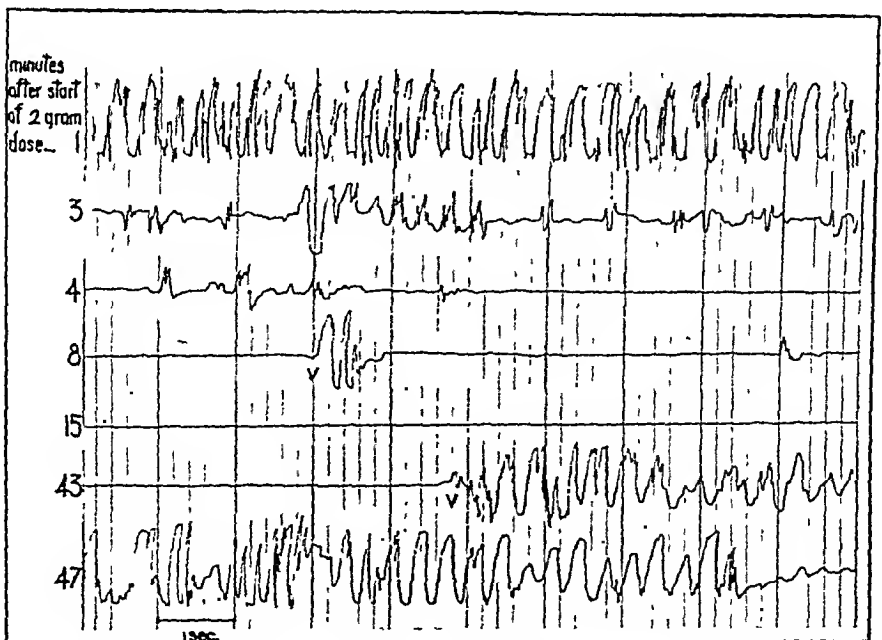


FIG. 2.—The effect of myanesin upon involuntary choreo-athetotic movement in a case of Wilson's disease (Hepato-lenticular degeneration). A fixed photo-electric cell is activated by a light attached to subject's finger and the potential lead into a standard electroencephalograph amplifier. Record continuous in each line beginning at stated minutes after start of intravenous infusion of myanesin. In lines 4 and 6 the V indicates voluntary movement intended to provoke the choreoathetosis. Movements suppressed about 40 minutes. Infusion lasted 12 minutes. Time 1 sec.

(Figs. 1 and 2). Rigidity was greatly decreased or abolished in these cases, but strength was unaltered and tendon reflexes were little affected. Senile tremor was greatly improved. On the other hand, the intention tremor of multiple sclerosis was increased (in 2 cases). Two cases of chorea (1 Huntington's and 1 congenital) were unaltered. Brief discharges associated with anterior horn cell disease were unaf-

the exaggerated second-pain in response to pinprick of a tabetic was reduced, without loss of pinprick perception. Causalgic pain was relieved (1 case) for a short time and improved for 24 hours. Phantom limb pain, in contrast, was unaffected (1 case). Stephen and Chandy, and Schlesinger *et al.* had noted an effect upon pain.

These clinical observations suggest that myanesin in the doses used, has

TABLE 1.—EFFECT OF MYANESIN ON HANDGRIPS  
DYNAMOMETER READINGS AFTER MYANESIN

Case	Number of Trials in Parenthesis		After Drug	
	Average Reading	Range	Average Difference from Control 10 Min.	20 Min.
1. Facial Tic	53 (2)	+5 to -3	-3 (1)	0 (1)
2. Multiple Sclerosis	53 (2)	+7 to -8	+2 (1)	0 (1)
3. Multiple Sclerosis	20 (2)	0	0 (2)	-5 (2)
4. Parkinsonism	26 (10)	+5 to -6	+2 (3)	-1 (3)
5. Choreo-Athetosis	42 (5)	+3 to -2	+1 (2)	+1 (3)
6. Wilson's Disease	61 (7)	+19 to -16	+6 (3)	0 (4)
7. Tabes	94 (7)	+36 to -14	-19 (8)	-18 (5)

ected; we observed no alteration of organic facial hemispasm or of fasciculations in amyotrophic lateral sclerosis. In 1 case of tetanus the spasms were abolished.

Strength was unaltered in 16 cases without pre-existing weakness (Table 1), but 2 cases of multiple sclerosis developed a profound increase in weakness in the lower extremities although the upper extremities were unaffected. At the same time there was a decrease in tone. One tabetic had an increase in his ataxia and perhaps some decrease in strength. It is apparent that weakness is more easily developed in the presence of pre-existing disease of the pyramidal, and possibly other, systems.

Spontaneous pain was abolished and

a differential action upon the basal ganglia, brain stem and perhaps thalamus.

To test further the possibility that pathological discharges from thalamus or related structures might be influenced by this agent, we have studied the electroencephalograms of petit mal cases, in which large areas of brain cortex are "fired" simultaneously, possibly from thalamic or subthalamic nuclei<sup>6,7,8</sup>. In 6 cases of true petit mal without general seizures these discharges were abolished by this agent (Figs. 3 and 4). By contrast, convulsive cases with focal cortical abnormalities and 2 cases of petit mal associated with generalized seizures, the so-called "petit mal variant" of Lennox, and supposedly the result of cortical

damage, were unaffected. These observations, taken with the fact that normal electroencephalographic patterns were unaltered by this dose, suggest that myanesin acts in these cases by preventing the discharges arising in subcortical nuclei.

Since improvement in certain psychoses has been obtained by severing the connections of the thalamic nuclei and various parts of the cortex<sup>4</sup> or by a destruction of thalamic nuclei,<sup>13</sup> a trial of this agent which appears to

Although said to be effectual orally and intramuscularly in animals, we have used the intravenous route. Injection of a 1 or 2% solution rapidly up to 1 gm. establishes the action. From this dose the effect lasts a matter of a few minutes to 1 hour. To maintain action after the initial dose it is necessary to infuse at about 1 mg. per kilogram body weight per minute. This is about the amount required to maintain a constant blood level in animals.<sup>12</sup> It seems likely that effective action

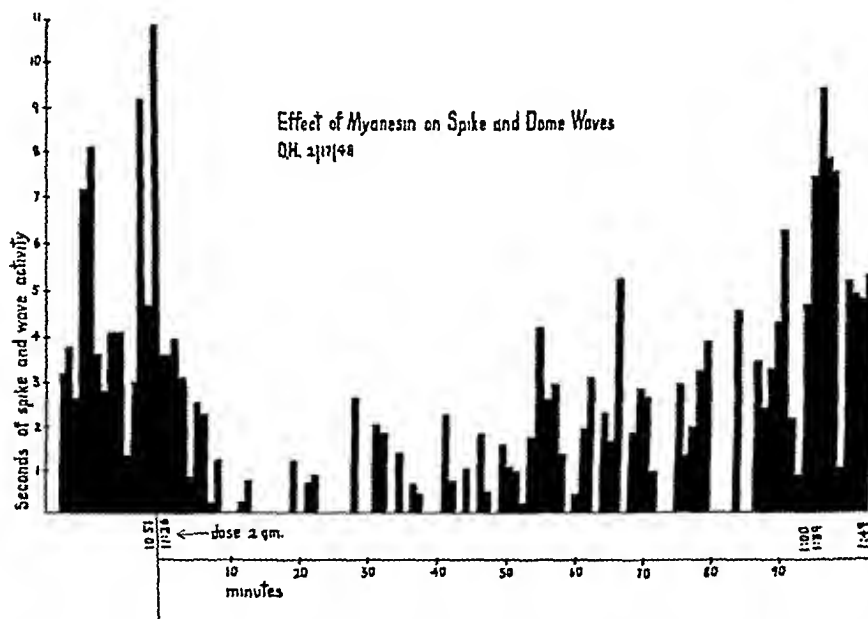


FIG. 3.—Effect of myanesin on electroencephalograph of true petit mal. The line in each minute occupied by spike and dome formations is indicated on ordinate. Record continuous. Dose 2 gm. at 11:26. Minutes after infusion indicated on abscissa. A sharp drop in activity lasts about 60 minutes.

affect the thalamus would seem to be profitable. Preliminary observations on 3 cases have proved of interest. A patient with reactive depression was improved for the period in which the drug was active; a deteriorated negativistic schizophrenic became communicative for the first time in years; and an agitated patient who would not respond became calm and communicative under the action of the drug. These experiences are being extended.

requires the maintenance of a critical blood level of an agent which is rapidly inactivated. The maximum total dose we have used is 87 mg. per kilogram body weight.

We have observed no untoward reactions. Although the drug is hemolytic we have found no hemoglobinuria. Jacobs *et al.*<sup>5</sup> find that it acts as a detergent on red cells. We have observed no local venous thrombosis.

The action of myanesin appears to

be differentially selective for the cluster of subcortical nuclei which make up the basal ganglia, thalamus and brain stem. With increasing dosage the conducting mechanisms of the spinal cord, both motor and sensory, are blocked, and cortical activity is depressed. Finally, a peripheral neuromuscular block ensues. But apart from this selective affinity of action, the evidence from pathological cases suggests that the drug cuts down any repetitious, prolonged or grouped discharge.

relief of pain. Examples are: as an adjunct to anesthesia and, as Schlesinger *et al.* suggest, for painful lumbar spasm and manipulation of joints. In the case of Parkinsonism rigidity and tremor and athetosis the drug unquestionably has a greater effect than any other therapy short of narcosis. This fact alone should encourage a search for similar, but longer-acting compounds. The rapid inactivation of the drug still limits its usefulness in chronic conditions.

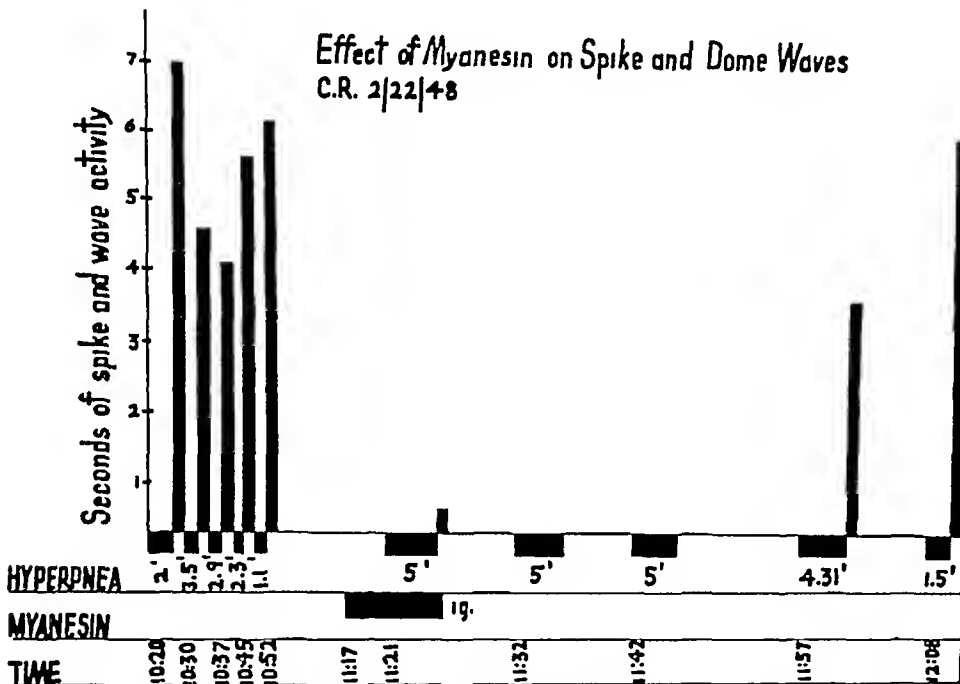


FIG. 4.—Preparation of graph similar to Fig. 3. Bursts of spike and dome waves were provoked by hyperpnea. In each control trial they appeared within 3.5 min. Five minute hyperventilations 4, 15 and 25 min. after start of infusion did not produce bursts until 40 minutes after infusion when they reappeared.

Tremor, athetosis, rigidity, spasticity, the spasm of tetanus, and prolonged pain, all may be abolished by myanesin at a time when brief twitches, such as choreic jerks and fasciculations and the perception of pinprick are unimpaired. This, in turn, may depend, as with barbiturates, upon a depression of synaptic transmission.

As matters now stand, myanesin may be used, wherever intravenous infusion is feasible, to achieve a transitory relief of tremor, relaxation of tone, and

**Summary.** Myanesin, an alpha substituted glycerol, which was found by Stephen and Chandy to have a depressant action on the parts of the nervous system lying between the cortex and the spinal cord, was administered to a variety of pathological cases in order to analyze its action and to test its therapeutic possibilities. With intravenous dosage the effect is quite transitory, lasting from a few minutes to a few hours.

Parkinsonian tremor is abolished



without impairment of strength or consciousness, an action which is unique. Choreo-athetosis is reduced or abolished, confirming other observations. Senile tremor is improved but the tremor of multiple sclerosis was increased. Chorea (Huntington's and congenital) was unaffected. Brief discharges associated with anterior horn cell disease were not affected as in fasciculations of amyotrophic lateral sclerosis and organic facial hemispasms. On the other hand, the spasm of tetanus was abolished.

The tone of Parkinsonian cases was reduced. Strength was unaltered with the dose used except in the presence of pre-existing lateral column disease.

A sensory effect was noted in the

abolition of tabetic pain and an exaggerated second pain response, and in causalgic pain. Phantom limb pain was unaltered.

These observations suggested a differential depression of function in the basal ganglia, brain stem and thalamus. This conclusion was strengthened by the abolition of petit mal discharges by a dose which did not affect the normal electroencephalogram or the discharge from a cortical scar.

In view of the results of thalamotomy and prefrontal lobotomy, the agent was tested on certain psychotic cases with promising results. This aspect of its action is being studied further.

The transitory action of the drug limits its therapeutic possibilities.

We wish to express our appreciation to Dr. Donald S. Searle of Burroughs Wellcome Company and Dr. H. Sidney Newcomer of E. R. Squibb & Sons Co., for part of the drug used — also to Dr. Sidney J. Deichmann and Dr. Harvey Bartle for their cooperation.

Addenda. The characteristic myanesin action can be obtained from oral medication. Repeated trials on 8 cases of Parkinsonism resulted in moderate relief of tremor for 30 to 60 minutes following 2 to 3 gm. doses. Occasionally the larger dose was ineffectual, and inconstant responses frequently occurred from similar doses.

No decrease in effect occurred in 2 subjects taking 3 gm. twice daily for 1 month; and in another a constant effect on tremor was attained throughout 4 hours of continuous intravenous infusion. A continued reduction of spasticity could be obtained by an hourly dosage of 2 gm. throughout a 2 week period, in a patient with post-encephalitic tetraplegia.

A drop in the leukocyte count to 3000 occurred in 2 subjects following large doses of myanesin. This effect is being investigated further.

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# THE TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH MASSIVE DOSES OF SYSTEMIC PENICILLIN

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PENICILLIN gives better results in pneumococcic meningitis than any other therapeutic agent yet discovered. Among the 40 patients treated in our clinic with sulfonamides alone, 93% died<sup>31</sup> while only 62% died among the 66 patients who received a combination of sulfonamides and penicillin. Other investigators have obtained case fatality rates with the use of penicillin ranging from 8% to 64%. By tabulating the series of cases containing 5 or more patients, we were able to find 319 cases of pneumococcic meningitis in the literature in which penicillin was the mainstay of treatment.<sup>2,3,9,10,12,14,15,29,33,36, 37,38</sup> Most of these patients received sulfonamides in addition and almost all of them received penicillin by both the intrathecal and intramuscular or intravenous routes. Death occurred in 157 cases, giving an average case fatality rate of 49.2%. This compares favorably with an average case fatality rate of 94% found among all the patients treated with sulfonamides in the District of Columbia for 4 years.<sup>5</sup>

The orthodox regimen for the treat-

ment of pneumococcic meningitis at the present time consists of daily intrathecal injections of 10,000 to 20,000 units of penicillin in conjunction with 200,000 to 1,000,000 units daily in divided doses systemically. Sulfadiazine or sulfamerazine is usually given in addition. When evidences of subarachnoid block appear, intraventricular or intracisternal injections of penicillin are recommended. In addition to the fact that only 51 recover among every 100 patients subjected to this type of treatment, the regimen itself has several disadvantages:

(1) Local instillation of penicillin may cause an irritative arachnoiditis, manifested by pleocytosis<sup>30</sup> and sometimes by subarachnoid block. The latter may require intraventricular and cisternal injection of penicillin with their attendant dangers or may result in hydrocephalus.

(2) Myelitis and radiculitis following intrathecal administration have been reported by several observers.<sup>7,32,34,35</sup> Clinical and experimental studies have demonstrated that when penicillin is

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applied to the cerebrum, areas of necrosis may be produced<sup>40</sup> and convulsions may occur.<sup>22,24,35</sup>

The distribution of penicillin throughout the cerebrospinal fluid is not always assured when it is injected intrathecally. McCune and Evans<sup>20</sup> reported in one instance that only a trace of penicillin had reached the right ventricle 2 hours after 7500 units had been introduced into the lumbar subarachnoid space. This is in contrast with the fact that when penicillin is administered systemically the concentration in the lateral ventricle is higher than that found in the lumbar intrathecal space, as shown by two of us with Dumoff-Stanley.<sup>6</sup>

Certain other disadvantages accompany the direct injection of penicillin into the cerebrospinal fluid. One of these is the danger of infection following lumbar puncture.<sup>11</sup> Another is the amount of work required on the part of physicians and attendants in doing repeated lumbar punctures, and the discomfort and annoyance to the patient resulting from these procedures.

Intrathecal penicillin is almost universally advocated for the treatment of pneumococcic meningitis because many investigators<sup>1,8,13,16,23,27</sup> have found that when penicillin is administered systemically, none diffuses into the cerebrospinal fluid. On the other hand, there are some reports<sup>4,6,17,19,21,28</sup>

TABLE 1. PATIENTS WITH PNEUMOCOCCIC MENINGITIS TREATED WITH ONE MILLION UNITS OF PENICILLIN EVERY 2 HOURS

Patient	Age (yrs.)	Type of Pneumococcus	Associated Infections	Day of Illness Treatment Begun	Duration of Penicillin Treatment (days)	Sulfonamides	Intrathecal Penicillin	Result	TREATMENT	
									Day Temperature Dropped 101°F.	Day WBC Below 30
Baby Sh.	3 days	8	No focus found	?	<1 day	0	0	D	—	—
J. F.	8 mos.	14	?	?	<1 day	1 dose	0	D (2½ hrs.)	—	—
J. G.	10 mos.	12	pneumonia	2	7 hrs.	Yes	0	D (7 hrs.)	—	—
M. H.	2 yrs.	7	head injury	2	6 days	Yes	0	R	5	6
P. A. W.	2 yrs.	14	pneumonia	1	7 days	0	0	R	3	7
G. T.	33 yrs.	13	?	?	10 days	Yes	1	R	2	19
P. M.	38 yrs.	10	pneumonia empyema endocarditis	?	9 days	Yes	0	D	—	—
H. L.	40 yrs.	22	?	?	12 days	Yes	0	R	2	5
L. S.	40 yrs.	4	?	18	13 days	Yes	Yes	R	3	32
A. R.	41 yrs.	8	pneumonia	4	7 days	0	0	R	4	19
L. H.	43 yrs.	8	otitis	4	13 days	Yes	0	R	4	4
T. O.	47 yrs.	12	?	?	16 days	0	0	R	4	8
V. A.	49 yrs.	12	arthritis	3	21 days	Yes	0	D	—	—
D. G.	52 yrs.	7	?	2	<1 day	Yes	0	D (11 hrs.)	—	—
A. C.	56 yrs.	not typed	otitis	?	9 days	0	0	R	2	4
N. V.	56 yrs.	8	endocarditis	11	<1 day	Yes	Yes	D (13 hrs.)	—	—
W. H.	56 yrs.	12	pneumonia arthritis	5	17 days	Yes	0	R	7	15
F. A.	57 yrs.	20	pneumonia	5	<1 day	Yes	Yes	D (6 hrs.)	—	—
M. B.	68 yrs.	23	?	?	7 days	0	0	R	3	10
G. L.	80 yrs.	9	?	4	7 days	0	0	R	2	8
W. R.	81 yrs.	18	No focus found	?	17 days	0	0	R	21	28

which indicate that low concentrations of the antibiotic are found in the cerebrospinal fluid, especially when fairly large doses are given systemically, particularly when meningitis is present. When Schwemlein and his co-workers<sup>31</sup> reported that detectable concentrations of penicillin were present in 100% of patients who received 20,000,000 units or more of penicillin during the course of 24 hours by continuous intravenous injection, we decided to treat patients with 1,000,000 units of penicillin intramuscularly at 2-hour intervals.

The concentration of penicillin in the blood and cerebrospinal fluid was determined in the case of 21 patients,

dose of 20,000 units of penicillin and 1 an intrathecal dose of 25,000 units. Thirteen patients were given sulfonamides in addition to penicillin. Eight patients died, 6 of them within 24 hours of the start of therapy. Penicillin therapy was continued for approximately 1 week after the temperature made its principal fall and the signs of toxicity began to recede, provided that the cerebrospinal fluid findings were improving. The duration of penicillin therapy in the 13 patients who recovered was as follows: 1 patient, 6 days; 3 patients, 7 days; 1 patient, 9 days; 1 patient, 10 days; 1 patient, 12 days; 3 patients, 13 days; 1

TABLE 2. RESULTS OF TREATMENT ACCORDING TO AGE

	Patients Treated with Penicillin Systemically and by Multiple Intrathecal Injections		Patients Treated with Massive Doses of Penicillin Systemically	
	Total	Died	Total	Died
0—1 Yr.	4	3	3	3
1—5 Yrs.	2	0	2	0
6—10 Yrs.	0	0	0	0
11—20 Yrs.	4	1	0	0
21—30 Yrs.	3	2	0	0
31—40 Yrs.	11	7	4	1
41—50 Yrs.	17	11	4	1
51—60 Yrs.	10	6	5	3
61—70 Yrs.	11	8	1	0
71— Yrs.	4	3	2	0
	66	41 (62%)	21	8 (38%)

with and without meningitis, at various intervals after beginning the administration of the antibiotic. Small amounts of penicillin were present in all patients within 60 minutes after intramuscular injections were begun. After 8 hours the spinal fluid concentrations were between .08 and 1.25 units per cc. The concentration of penicillin in the blood immediately prior to an injection (*i.e.*, 2 hours after the previous injection) varied between 2.5 and 20 units per cc.

We have treated 21 patients with pneumococcic meningitis, using doses of 1,000,000 units of penicillin every 2 hours (Table 1). Two of these patients were given a single intrathecal

patient, 16 days and 2 patients, 17 days.

The effects of treatment can best be evaluated by comparing these patients with the 66 patients who have been treated by us with multiple intrathecal doses of penicillin. All except 5 were given systemic penicillin concomitantly in doses which varied from 120,000 units to 3,000,000 units per day. All except 3 of these patients received full doses of sulfonamides systemically in addition. The 2 groups were quite similar in all respects. As shown in Table 2, both series contained a large number of patients who were in age groups where the prognosis is unfavorable. The proportion of patients under 1 year of age

or over 40 years was 70% and 71% for the "multiple intrathecal series" and the "massive systemic series" respectively. From Table 3 it will be seen that the source of the infection was approximately the same in both series.

**Results.** Among the 21 patients treated with massive doses of penicillin systemically, 8, or 38%, died. This may be contrasted to 41 deaths among the 66 patients who received multiple intrathecal injections, a case fatality rate of 62%. These differences are not quite statistically significant

had azotemia. He died 12 days after the temperature fell and 32 days after the start of treatment and was found at necropsy to have a malignant tumor of the left kidney with bony metastasis and no meningitis. The median day on which the temperature fell below 101° F. was the second day of treatment. In the same figure, the time of temperature fall has been charted for the last 19 patients who recovered in the series of patients who received multiple intrathecal injections. Although the temperature fell rapidly in the case of some patients, in half it

TABLE 3. RESULTS OF TREATMENT ACCORDING TO SOURCE OF INFECTION

	Patients Treated with Penicillin Systemically and by Multiple Intra- theal Injections		Patients Treated with Massive Doses of Peni- cillin Systemically	
	Total	Died	Total	Died
Pneumonia.....	23	16	5	2
Otitis and/or Mastoiditis.....	14	5	2	0
Endocarditis.....	2	2	2	2
Head Injury.....	1	0	1	0
Source not determined....	26	18	11	4
	66	41	21	8

when tested with the Yates modification of the Chi square method. Nevertheless, there are other factors which make it appear that the use of massive systemic doses is superior. If the patients who died within the first 24 hours of the start of penicillin therapy are excluded, 2 among 15 patients receiving massive systemic doses died (13%), and 33 among 58 receiving multiple intrathecal injections (57%). This difference is statistically significant.

Among the patients who recovered, the patients who received the massive doses of penicillin systemically had a more rapid drop in temperature. As shown in Figure 1, the temperature was below 101° F. in 12 of the 13 patients by the 7th day after the start of treatment. The 1 patient who had fever above this point for 21 days also

took 2 weeks or longer to drop below 101° F. The median for this group was 8 days.

One disturbing factor in the treatment of meningitis with frequent intrathecal injections has been a prolonged duration of pleocytosis. The arbitrary level of cerebrospinal fluid leukocytes which we have used as a criterion for discharging the patient has been 30 per cubic millimeter or below, provided that all of the cells are lymphocytes. In Figure 2 are shown the days on which the cells first reached this level. Among the patients treated with massive systemic doses the duration of pleocytosis extended from 4 to 32 days, with a median of 8 days. It is interesting that the patient who continued to have an increased spinal fluid leukocyte count for 32 days was the one patient in the recovered group



sibly this might be accomplished by giving an initial intravenous injection of 1,000,000 units over the course of 3 or 4 hours. Until a suitable method is devised for this purpose, it may be the wisest policy to give a single initial intrathecal injection of 20,000 units of penicillin as soon as the diagnosis of pneumococcic meningitis is made, to all patients in coma and others who appear to be in extremis. In the other patients we believe it is advisable to refrain from giving intrathecal peni-

possibility of employing similar large doses in infections in serous cavities where diffusion is inadequate with the doses of penicillin ordinarily used.

Sulfonamides do not appear to have any value as adjuvants when these large doses of penicillin are used. Sulfonamides were given to 13 of our patients, 7 of whom died. The main reason for employing these drugs in conjunction with penicillin, namely, that they diffuse so well into the cerebrospinal fluid, apparently has no sig-

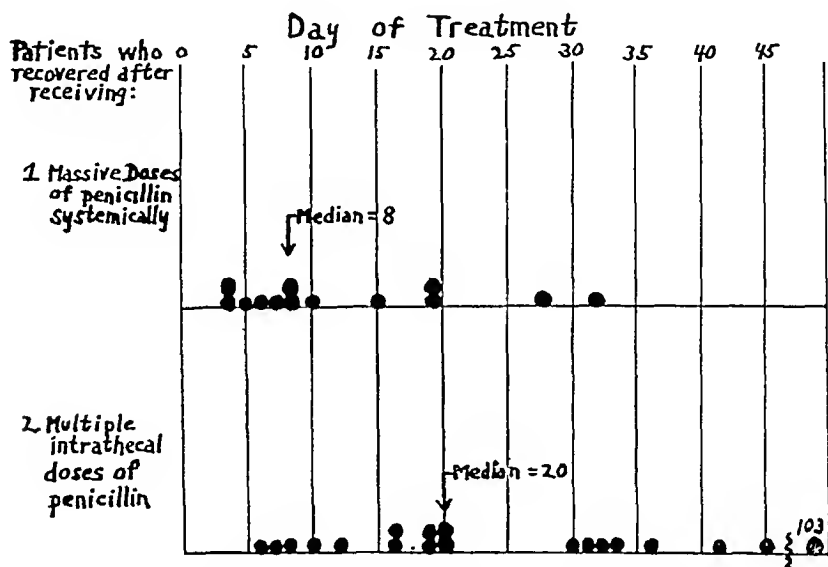


Figure 2—Day on which the cerebrospinal fluid leukocyte count fell to 30 per cubic millimeter or below, in the patients who recovered.

cillin, since even a single dose may increase the duration of pleocytosis and damage in the form of subarachnoid adhesions.

This method of therapy may be applicable to other types of purulent meningitis such as the staphylococcic and streptococcic varieties. We have had an opportunity to use this regimen in only 1 infant with meningitis caused by the hemolytic streptococcus. The patient recovered. The good results obtained in pneumococcic meningitis may also justify a re-evaluation of the

nificance when doses of penicillin are employed which insure the proper diffusion of the antibiotic.

**Summary and Conclusions.** 1. Twenty-one patients with pneumococcic meningitis have been treated with 1,000,000 units of penicillin intramuscularly every 2 hours. Three of them received a single intrathecal injection of penicillin; the others were given no intrathecal therapy. Thirteen patients received sulfonamides in addition. There were 8 deaths, a case fatality

rate of 38%, compared with 41 deaths (62%) among the 66 patients previously treated by us with smaller doses of penicillin systemically plus repeated intrathecal injections of penicillin.

2. In the patients who recovered, the temperature dropped more rapidly among those who received massive systemic doses than among those who were given repeated intrathecal injections. Likewise the duration of pleocytosis was shorter in the former group.

3. Since the results of massive systemic penicillin therapy in pneumo-

coccic meningitis are at least as good and apparently better than those obtained with the conventional systemic doses of penicillin plus multiple intrathecal doses, it is recommended that all patients with pneumococcic meningitis be given 1,000,000 units of penicillin intramuscularly at 2 hour intervals. Patients in coma or in extremis when treatment is begun may be given a single initial intrathecal dose of penicillin in addition. Sulfonamides do not appear to be necessary when these doses are used.

We wish to thank Mrs. Joan R. Broyhill and Miss Myrtle Meyer for technical assistance.

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# PENICILLIN SYPHILOTHERAPY ADMINISTERED DURING PREGNANCY A STUDY OF 149 PREGNANCIES DURING WHICH PENICILLIN WAS GIVEN FOR EARLY MATERNAL SYPHILIS

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Most workers in the field regard penicillin as the treatment of choice for the syphilitic pregnant woman because of its lack of toxicity, the high proportion of satisfactory results obtained, and the brevity of treatment.<sup>1,2,3,4,7,8,10,11,12</sup> It has been recommended that in this situation the older methods of therapy be abandoned. Our experience has grown since 1946<sup>4</sup> to include 149 women with early syphilis who have been treated with penicillin during pregnancy. It is the purpose of this brief paper to present the results obtained, in terms of maternal and fetal outcome, and to emphasize further the desirability of penicillin treatment for the syphilitic pregnant woman.

**Material and Methods.** Between October, 1943, and March, 1948, 149 women were treated with penicillin for concomitant early syphilis and pregnancy in the Johns Hopkins Hospital.† Twenty-three of these were white; 126 (85.6%) were Negroes. The original diagnosis in 70 patients (47.0%) was primary and/or secondary syphilis. In the majority of these *Treponema pallidum* were demonstrated under the darkfield microscope. The remainder had early latent or early asymptomatic neurosyphilis of less than 2 years' duration.

As soon as the diagnosis of concomitant pregnancy and untreated early syphilis was established, each woman was given treatment with penicillin. In several, especially early in the study when comparatively small total amounts of penicillin were administered (that is, less than 3 million units), mapharsen (ap-

proximately 300 mg.) and bismuth (approximately 600 mg.) were given concurrently. When treatment had been completed, each patient was followed monthly in a special prenatal clinic. Complete examination of the skin and mucous membranes and quantitative serologic evaluation were carried out at each visit, in addition to routine prenatal care. In the event lesions of mucocutaneous relapse (or reinfection) were encountered, if the titer remained at a high level after treatment (seroresistance), or showed a marked and sustained rise (serorelapse), retreatment with penicillin was instituted immediately. After retreatment, the monthly clinic visits were resumed.

Offspring of these mothers were followed at monthly intervals for from 4 months to a year or longer in the Family Syphilis Clinic of the Johns Hopkins Hospital with titrated serologic tests and complete physical examinations. Roentgenograms of the long bones were obtained one or more times in approximately one-third of these babies.

Maternal syphilotherapy, for the majority of these patients, consisted of amorphous or crystalline penicillin G only; 40% received the latter preparation. No difference in outcome in the 2 groups was noted. Although all women requiring retreatment had originally been given amorphous penicillin, such "treatment failures" were attributed more to the comparatively small total doses these women received than to the penicillin preparation itself. In Table 1 are presented the amounts of antibiotic administered to these women in relation to the month of gestation when therapy was begun.‡ In all patients treated during pregnancy the antibiotic was given in aqueous solution, intramuscularly, at intervals of every 2 or 3 hours over a period of 7.5 to 15 days on an in-patient basis.

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† Of these, 34 have since been followed through one or more subsequent pregnancies without additional syphilotherapy and have been described in a separate communication.<sup>13</sup>

‡ Women requiring retreatment were entered in the Tables according to the total amount of penicillin received during pregnancy and month of gestation the last course of penicillin was administered.

Results. The outcome of each of the 149 pregnancies is tabulated in Table 2. Congenital syphilis was found in none. The single neonatal death, due to sickle cell anemia, occurred in a full-term Negro infant. One abortion took place in the 15th week of pregnancy, the other 4.5 months after conception. In neither was there evidence of syphilis and both mothers had completed syphilotherapy prior to these disasters. These women, as well as the mothers of 10 of the premature infants, were

patient had been given 9.6 million units of amorphous penicillin in peanut oil-beeswax; serorelapses during pregnancy required 4.8 and 6.1 million units of penicillin G in the 2nd and 9th months of pregnancy, respectively. Two other women, following 0.6 and 2.4 million units of amorphous penicillin in the 2nd and 4th months of gestation, underwent serorelapse and required 1.2 and 3.1 million units of additional amorphous penicillin during the 5th and 9th months, respectively. In all other

TABLE 1.—PENICILLIN SYPHILOTHErapy GIVEN TO 149 WOMEN, BY MONTH OF GESTATION DURING WHICH TREATMENT WAS STARTED.

Total amount penicillin administered (millions of units)	Number of patients	Month of gestation									
		1	2	3	4	5	6	7	8	9	
0.6 to 1.0	1	-	-	-	1	-	-	-	-	-	
1.0 to 2.0	19	2	1	3	4	4	1	2	2	-	
2.0 to 3.0	25	-	1	3	1	3	8	4	2	3	
3.0 to 4.0	8	1	2	-	2	-	-	1	1	1	
4.0 to 5.0	91	-	3	5	9	17	20	15	12	10	
> 5.0	5	-	-	1	-	1	-	-	-	3	
Total	149	3	7	12	17	25	29	22	17	17	

originally treated for primary and, or, secondary syphilis. In none of the 16 infants born prematurely could either maternal disease or penicillin therapy be incriminated as the cause of prematurity. The incidence of prematurity in this study (10.7%) probably did not differ significantly from the expected incidence in a similar but non-syphilitic group of mothers<sup>1</sup>.

Indication for retreatment arose in 6 pregnant women (4%). Two women originally treated prior to these pregnancies with 3.6 and 0.8 million Oxford units, underwent serorelapse. Retreatment with 3.6 million units of amorphous penicillin during the 5th and 7th months of pregnancy, respectively, effectively prevented (or cured) congenital syphilis in the offspring. Another woman, treated prior to pregnancy with 2.4 million units, required retreatment with 4.8 million units of penicillin G because of infectious relapse (reinfection?) during the 3rd month of gestation. One non-pregnant

patients, the intensive routine of prenatal examinations did not disclose indications for retreatment.

Data concerning the maternal titer and the serologic titer of the infant's cord blood were available in 67 records. In 24 of these the mother was seropositive, the cord blood negative; the maternal titer was, as a rule, in the range of 1 to 8 Eagle units. In 30 records the maternal and cord blood determinations were both positive. In 2 of these the maternal and infantile titers were identical but in the remainder the cord blood titers were lower than the maternal ones, which tended to be in the range of 4 to 16 Eagle units or higher. Twelve mothers who were seronegative had seronegative babies and in a single instance such a mother had a seropositive baby. Repetition of this infant's serologic test in the first week of life yielded a negative test which was repeatedly confirmed thereafter. These resembled data reported by others<sup>2,10,12</sup>.

Of those born alive, 48 infants (32.6%) were seropositive in the cord blood or at the time of the first visit to the Family Syphilis Clinic. In many of these it was impossible to tell when reversion to negative took place, within wide limits, because of long intervals between examinations. Two, however, were seropositive when tested between 71 and 80 days after birth and reverted during the next 10-day period. The most persistent seropositivity was exhibited by a Negro baby whose mother

probably occurred in these babies, but that the penicillin administered to the mother had effected cure of the fetal disease. These data, together with the unusual serologic findings mentioned previously, will be elaborated in a later communication<sup>5</sup>.

**Discussion.** Data obtained in this study support strongly the belief that penicillin is the treatment of choice for the syphilitic pregnant woman. These results, obtained in women with syph-

TABLE 2.—CLASSIFICATION OF PROGENY OF 149 MOTHERS, BY AMOUNT OF PENICILLIN SYPHILOTHERAPY GIVEN DURING PREGNANCY.

Total amount penicillin administered (millions of units)	Non-syphilitic				Syphilitic
	Full term	Premature	Abortion	Neonatal death	
0.6 to 1.0	1	-	-	-	-
1.0 to 2.0	13	3	2	1	-
2.0 to 3.0	23	2	-	-	-
3.0 to 4.0	6	2	-	-	-
4.0 to 5.0	84*	8	-	-	-
> 5.0	4	1	-	-	-
Total	131	16	2	1	0

\*Including one set of twins

(treated during the 5th month of pregnancy) had a titer of 32 Eagle units at the time of delivery; the cord blood was positive in a titer of 8 units. Nine subsequent serologic tests were positive, in gradually falling titer, the last one being obtained 101 days after birth. When next examined, 20 days later, he was seronegative. Several roentgenograms of the long bones were normal and he has remained clinically well throughout the first year of life. Every survivor in this group of infants born of penicillin-treated mothers with early syphilis had become seronegative by the end of the 4th month of life.

One or more roentgenograms of the long bones were taken in 54 infants. In the majority of these (77.8%) the osseous structures were described as normal. In 12 infants, however, changes compatible with osseous congenital syphilis were noted. These findings were interpreted by us as healing or regressing lesions and were considered evidence that *in utero* infection had

ilis of less than 2 years' duration are entirely applicable to those with late syphilis<sup>4</sup>. Since penicillin, like arsenic and bismuth, has been repeatedly shown to penetrate the placental barrier at any time after the 10th week of gestation, it is reasonable to assume that the antibiotic, administered to the mother may function either to prevent transmission of the disease to the fetus or to effect cure of the fetus once congenital syphilis has been established<sup>12</sup>. Three lines of evidence support the contention that the fetal disease may be cured as well as prevented:

It made no difference when in pregnancy penicillin was administered (see Table I), in so far as the incidence of infantile congenital syphilis was concerned<sup>8</sup>. In this study, 73.4% of the patients were treated during or after the 5th month of gestation. Although these fetuses may have been infected, syphilotherapy after birth was necessary in none.

The second observation showing that

in utero disease may be attacked by maternal penicillin treatment, was that infants born of 12 mothers (all treated during or after the 5th month) had radiographic changes compatible with the residuals of osseous congenital syphilis<sup>6</sup>. All remained clinically well in the absence of syphilotherapy, and all became seronegative within the first 4 months of life.

The third factor was that several of the infants exhibited a marked persistence of reagin. This phenomenon has recently been encountered by other workers<sup>12</sup>. Ordinarily, "the maximum length of time for which maternal reagin has been observed to persist in the blood of a normal infant is 70 days"<sup>9</sup>. In this series 2 infants were shown to undergo seroreversal between 81 and 90 days of life, and one between 101 and 121 days. This was interpreted by us as probably being due to additional reagin actively elaborated by these fetuses as a consequence of congenital syphilitic infection. Such infants would be analogous to adults treated for early acquired syphilis who usually require 6 months or longer to achieve seronegativity after adequate syphilotherapy.

Within wide limits, the total amount of antibiotic administered to the women in this series, or whether crystalline penicillin G was employed, did not appear to influence materially the outcome of pregnancy. On the other hand, no patient who was given 4 million units or more required retreatment. It is our feeling, therefore, that a total amount of penicillin of 4.8 million units or more, without supplementary metal chemotherapy, is entirely adequate for the treatment of early (or late) syphilis in the mother, the prevention of transmission of syphilis to the uninfected fetus, and the cure of congenital syphilis in the fetus if infection has already taken place. This statement implies

concentrated prenatal and post-partum follow-up care.

Relapse or reinfection may occur at any time and intensive follow-up routines should be adhered to in order to eliminate effectively congenital syphilis. Even though healthy babies may be born of mothers treated late in pregnancy, the presence of *T. pallida* in the fetuses for one or more months can do nothing but harm. Therapy should be instituted at the earliest possible moment after the discovery of relapse or reinfection in the pregnant woman. By prompt retreatment, damage to the fetus should be minimized.

**Summary.** Between 1943 and March, 1948, 149 women with concomitant early syphilis and pregnancy were treated with penicillin at the Johns Hopkins Hospital in total amounts ranging from 0.6 to over 5 million Oxford units. In all cases the antibiotic was given in aqueous solution, intramuscularly, every 2 or 3 hours for 7.5 to 15 days. Six women (4%) required retreatment with penicillin for relapse or reinfection, seroresistance, or serorelapse. Nearly three-quarters of all patients were treated after the 4th month of gestation.

Two abortions occurred; in neither could syphilis or maternal penicillin administration be implicated. Sixteen infants were premature but survived. The remainder were full-term infants, one of whom died of sickle cell anemia during the neonatal period. On the basis of clinical, serologic, and, or, roentgenologic evidence through the first 4 months of life or longer, treatment for infantile congenital syphilis was indicated in none.

These data furnished additional evidence that penicillin, combined with intensive post-treatment serologic and clinical study, is the current treatment of choice for the syphilitic pregnant woman.

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## NITROGEN MUSTARD THERAPY

### THE USE OF METHYL BIS ( $\beta$ CHLOROETHYL) AMINE HYDROCHLORIDE IN HODGKIN'S DISEASE, LEUKEMIA, LYMPHOSARCOMA AND CANCER OF THE LUNG

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THE first clinical trial of a nitrogen mustard as a therapeutic agent in the treatment of neoplastic diseases was made by Gilman, Goodman, Lindsborg and Dougherty<sup>1</sup> in 1942. These investigators administered tris ( $\beta$  chloroethyl) amine hydrochloride intravenously to 6 patients in the terminal stages of various neoplastic diseases. In 2 patients with lymphosarcoma, the drug caused a rapid dissolution of large tumor masses. These gratifying results led to the further clinical investigation of this drug and also of methyl bis ( $\beta$  chloroethyl) amine hydrochloride in neoplasms involving the lymphoid and hemopoietic tissues.<sup>2,3,4,5</sup>

This paper is concerned with the use of methyl bis ( $\beta$  chloroethyl) amine hydrochloride in cases of Hodgkin's disease, leukemia, lymphosarcoma and carcinoma of the lung. Eleven of these cases are included in a report which will be published by the National Research Council. In this communication observation on the use of the drug in 29 additional patients will be reported.

**Method.** Methyl bis ( $\beta$  chloroethyl) amine hydrochloride was administered intravenously at a daily dose of .1 mg. per kg. of body weight. A course of treatment consisted of 4 consecutive daily injections. When marked changes in the blood were noted, the course was interrupted and subsequent injections were given at intervals of 2 to 4 days. The solution was freshly made by injecting 10 cc. of a sterile isotonic solution of sodium chloride in a vial containing 10 mg. of the drug. The injection was given immediately after the solution was pre-

pared. In a few patients the injection was given directly into a vein with a syringe. In the majority of the patients the solution was injected with a rubber tubing during a course of saline infusion. Special care was taken to prevent extravasation of the solution and prolonged contact with the skin. Additional courses were given at 2 to 16 week intervals depending upon the response to the nitrogen mustard and the hematological effect. Complete blood counts were made before treatment and at frequent intervals after the injection. In selected patients repeated sternal marrow aspirations were performed.

**Results.** The pertinent data of each patient treated are tabulated in Table 1. A summary of the results of treatment in each group is given in Table 2.

*Hodgkin's Disease:* Thirteen patients with this disease were treated with nitrogen mustard; 11 had previously had Roentgen-ray therapy. In 11 of the 13 patients, the drug produced remissions lasting from 6 weeks to 19 months. Seven of the 11 patients were taken to be Roentgen-ray resistant. In these 11 patients, a course of nitrogen mustard resulted in a moderate to marked general improvement in health. The temperature was lowered or became normal, the appetite improved, the lymph nodes regressed, and pruritus diminished. In 3 patients the liver and spleen became smaller and in 2 patients the amount of involvement of lung parenchyma was reduced. The response was estimated as good in 6 and fair in 5 patients. One patient (Case 2) had Hodgkin's disease for 8

<i>Case</i>	<i>Name</i>	<i>Age</i>	<i>Sex</i>	<i>Duration of disease before HN<sub>2</sub>HCL therapy (mos.)</i>	<i>Previous therapy</i>	<i>Condition of patient before therapy</i>	<i>No. of courses given**</i>	<i>Duration of remission (range in mos.)</i>	<i>General response</i>	<i>Comments</i>
<b>HODGKIN'S DISEASE</b>										
1*	R.G.	31	F	24	x-ray	poor	3.25	1.5-2	fair	Died 9 mos. after initiation of treatment.
2*	N.B.	41	M	96	x-ray	poor	1	19	good	Continues in remission; returned to his occupation.
3*	G.K.	37	F	14	x-ray	fair	2	3-11	good	Continues in remission of 11 mos.; returned to her occupation.
4*	B.W.	46	M	84	None	fair	1	12	good	Continues in remission; returned to his occupation.
5	L.K.	42	M	30	x-ray	poor	4	2-6	fair	Died 10 mos. after initiation of treatment.
6	G.S.	38	F	25	x-ray	fair	2	4-7	fair	Continues in remission of 4 mos.
7	S.R.	44	M	36	x-ray	poor	3	1-3	fair	Continues in remission of 3 mos.
8	C.M.	39	F	48	x-ray	poor	1	None	poor	Died 6 wks. after initiation of treatment.
9	H.B.	53	M	21	x-ray	fair	2	3-5	good	Continues in remission of 5 mos.; returned to his occupation.
10	K.L.	25	F	5	None	poor	2	1-3	good	Continues in remission of 3 mos.; returned to her occupation.
11	L.B.	44	F	10	x-ray	poor	2	2-6	good	Continues in remission of 6 mos.
12	G.F.	48	M	18	x-ray	fair	1	3	fair	Continues in remission.
13	F.K.	49	M	60	x-ray	poor	1	—	poor	Died 1 mo. after initiation of treatment.
<b>CHRONIC LYMPHATIC LEUKEMIA</b>										
14	H.F.	54	M	21	x-ray	fair	2	3	fair	Failed to respond to a 2nd course; died 8 mos. after initiation of treatment.
15	D.G.	42	F	8	None	fair	1	7	good	Continues in remission.
16	A.M.	50	M	60	x-ray	poor	2	—	poor	Died 4 mos. after initiation of treatment.
17	S.J.	48	F	36	x-ray	fair	2	1.5	fair	Failed to respond to a 2nd course; died 4 mos. after initiation of treatment.
18	B.G.	68	M	42	x-ray	poor	1	—	poor	Patient still living; condition is poor.
<b>ACUTE LYMPHATIC LEUKEMIA</b>										
19	S.L.	42	M	2	None	poor	1	—	poor	Died 1 mo. after initiation of treatment.
<b>CHRONIC MYELOGENOUS LEUKEMIA</b>										
20*	E.H.	33	F	40	x-ray	poor	1	None	poor	Died 2 mos. after initiation of treatment.
					radio-active phosphorus					
21	A.R.	31	M	36	x-ray	poor	2	1.5	fair	Failed to respond to a 2nd course of HN <sub>2</sub> HCL; died 3 mos. after initiation of treatment.
22	B.J.	56	F	18	None	fair	1	None	poor	Patient is now receiving x-ray therapy.
23	H.S.	38	M	24	None	poor	2	2-3	fair	Continues in remission of 3 mos.
24	A.F.	40	F	53	x-ray	poor	3	None	poor	Died 2 mos. after initiation of treatment.
<b>LYMPHOSARCOMA</b>										
25	B.L.	40	M	20	x-ray	poor	2	—	poor	Died 2 mos. after initiation of treatment.
26	M.W.	18	F	6	None	fair	1	5	good	Continues in remission.
27	H.R.	63	M	15	x-ray	poor	2	—	poor	Died 4 mos. after initiation of treatment.
28	L.P.	28	M	12	x-ray	fair	1	3	good	Continues in remission.
29	F.G.	31	F	18	x-ray	poor	1	—	poor	Died 3 mos. after initiation of treatment.
<b>CARCINOMA OF THE LUNG (SQUAMOUS CELL)</b>										
30*	B.P.	65	M	10	None	fair	2	—	poor	Died 8 mos. after initiation of treatment.
31*	G.G.	47	M	8	None	fair	2	1.5	fair	Failed to respond to a 2nd course; died 7 mos. after initiation of treatment.
32*	A.H.	71	M	12	x-ray	poor	1	—	poor	Died 4 mos. after initiation of treatment.
33*	M.K.	55	F	18	None	poor	1	—	poor	Died 2 mos. after initiation of treatment.
34	H.T.	48	M	6	x-ray	fair	1	—	poor	Patient is still living; condition is poor.
35	F.M.	60	M	15	x-ray	fair	2	—	poor	Died 1 mo. after initiation of treatment.
36	A.C.	48	M	4	None	fair	1	—	poor	Patient now receiving x-ray therapy.
<b>CARCINOMA OF THE LUNG (ANAPLASTIC)</b>										
37*	S.W.	54	M	6	None	poor	2	3	good	Failed to respond to a 2nd course; died 5 mos. after initiation of treatment.
38*	H.N.	73	F	11	x-ray	poor	1	—	poor	Died 2 mos. after initiation of treatment.
39	F.O.	50	M	6	x-ray	fair	2	—	poor	Patient is still living; condition is poor.
40	G.D.	42	M	7	x-ray	poor	1	—	poor	Patient is still living; condition is poor.

\* Included in report to be published by the National Research Council

\*\* Course = 4 injections of 0.1 mg. per kg. for 4 doses



TABLE 2. SUMMARY OF RESULTS OF TREATMENT WITH NITROGEN MUSTARD

	Hodgkin's Disease	Leukemia Lymphatic	Myelogenous	Lympho- sarcoma	Cancer of the Lung
Total No. of Cases	13	6	5	5	11
Male	7	4	2	3	10
Female	6	2	3	2	1
Average Age (yrs.)	42	50	39.6	36	55.7
Range	25-58	42-66	31-56	18-63	42-73
Average Duration of Disease (mos.)	36	28.2	34.2	14.2	9.4
Range	5-96	2-60	18-53	6-20	4-18
No. Previously Treated with x-rays	11	4	3*	4	6
No. Initially Treated with HN <sub>2</sub> HCL	2	2	2	1	5
No. of Courses Given (Range)	1-4	1-2	1-3	1-2	1-3
Results					
Good	6	1	None	2	None
Fair	5	2	2	None	2
Poor	2	3	3	3	10
Average Duration of Remission (mos.)	4.8	3.8	2.1	4	2.2
Range	1.5-19	1.5-7	1.5-3	3-5	1.5-3
No. of Patients Living Since HN <sub>2</sub> HCL was Started	9	2	2	2	1
No. of Mos. Living Since HN <sub>2</sub> HCL was Started	3-18	2-7	1-3	3-5	2-4
No. of Patients Dead Since HN <sub>2</sub> HCL was Started	4	4	3	3	7
Duration of Life Since HN <sub>2</sub> HCL was Started (mos.)	1-8	1-4	2-3	2-4	1-7

One patient received radio-active phosphorus in addition to x-rays.

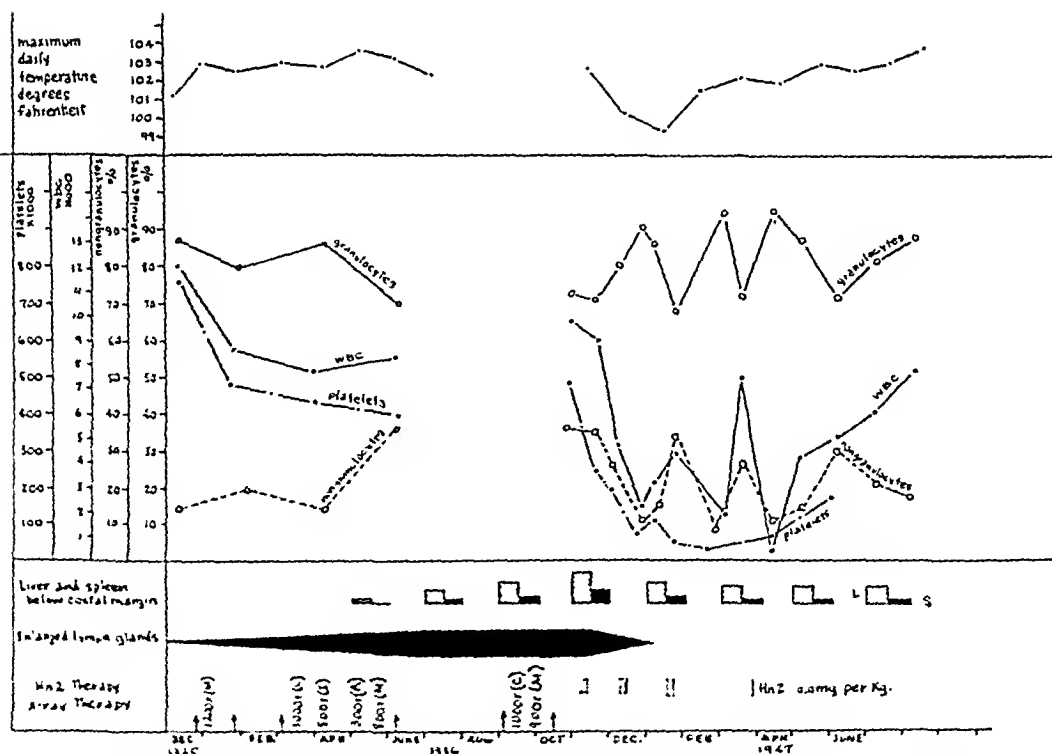


Fig. 1.—Course of a patient with Hodgkin's disease (case 1) under Roentgen-ray and mustard therapy. (M) = mediastinum, (C) = cervical; (I) = inguinal; (A) = axillary.

years and no longer responded to Roentgen-ray therapy. Before nitrogen mustard was given, this patient was an invalid because of paraplegia. One month after a course of nitrogen mustard the patient was able to return to his occupation. He is now in a remission which has lasted 19 months. Two patients who were treated in the late stages of the disease did not respond to nitrogen mustard. Two of the 11 patients who showed a response died of an extension of the disease within 9 to 10 months after nitrogen mustard therapy was begun. Five of the 11 patients are now able to carry on their occupations.

The following case history, although it does not represent the best results obtained from nitrogen mustard, is given because it illustrates the comparative effects of this drug and those of Roentgen rays in a patient with a virulent type of Hodgkin's disease.

**Case History:** Case 1. R. G., a 30 year old female was admitted to the Greenville Hospital on December 10, 1945, with the chief complaint of pruritus, cough, fever and weakness. One year prior to admission, the patient developed a generalized pruritus and felt weak. Ten months before admission, she began to have a fever for which she was given sulfa drugs. The fever, however, persisted and the pruritus increased in intensity until admission to the hospital.

Physical examination disclosed areas of pigmentation over the body and the extremities. A very small lymph node was felt in the right supraclavicular region. There was flatness to percussion below the angle of the right scapular. Vocal fremitus was absent over that area and the breath sounds were diminished. The heart was displaced to the left. The temperature was  $102.2^{\circ}$  and the pulse rate was 112.

The urine was normal.

A blood count showed hemoglobin 74%, red blood cells 4,200,000, white blood cells 11,400 (neutrophils 84%; lymphocytes 8%; monocytes 6%; eosinophils 1% and myelocytes 1%). The

platelet count was 780,000 per cu. mm. A chest plate showed a homogeneous density extending from the level of the 3rd rib to the base. Thoracentesis resulted in the removal of 1000 cc. of clear yellow fluid. A biopsy of the right supraclavicular gland showed Hodgkin's disease.

Radiation therapy was given during the period of December 20, 1945 to October 14, 1946 (Fig. 1). Following a course of 1200r to the mediastinum, the patient felt much worse. The cervical, axillary and inguinal glands became enlarged and the temperature was higher. She was then given 1000r to the right and left cervical regions, 500r to the right and left inguinal regions, 300r to the right and left axillary regions, and 800r to the mediastinum. The response was poor. In May, 1947, the liver and spleen became palpable. She received another course of 1000r to the right and left cervical regions and 900r to the mediastinum. The liver and spleen gradually became larger and the patient developed ascites and edema of the lower extremities.

Nitrogen mustard therapy was initiated on November 7, 1946. Methyl bis ( $\beta$  chloroethyl) amine hydrochloride, .1 mg. per kg. of body weight, was injected intravenously by the direct route for 4 consecutive days. Nausea and vomiting occurred 2 hours after the injection and lasted for 4 hours. Three days after the course was completed the temperature was lower and the appetite was improved. The peripheral glands began to regress. Another course of nitrogen mustard was given during the period of December 4 to December 7, 1946, inclusive. Following the second course, the temperature became normal and the enlarged lymph glands disappeared. The liver and spleen became smaller and the patient felt improved. The white count fell gradually and on December 10 there were 2050 leukocytes per cu. mm. The platelet count fell to 79,000 per cu. mm. One week later the leukocytes rose to 3100 per cu. mm. and the platelet count to 124,000 per cu. mm. In January 1947, the temperature began to rise again and the pruritus increased in intensity. A third course of nitrogen mustard was

started on January 17, 1947, and was given for 4 consecutive days. The response was fair and a remission was produced which lasted for 6 weeks. On March 21, 1947, she was given one injection of nitrogen mustard. The next day the leukocyte count fell to 300 per cu. mm. and the platelet count fell to 40,000 per cu. mm. There were 92% granulocytes and 8% nongranulocytes. Nitrogen mustard was then discontinued. The temperature remained high and the patient became confined to bed. There was, however, no lymphadenopathy. On April 14, the leukocyte count rose to 3850 per cu. mm. and the differential count showed 85% granulocytes and 15% lymphocytes. On April 18, a platelet count showed 120,000 per cu. mm. In May, 1947, hirsuties became a prominent feature. The patient became markedly cachectic, ran a downhill course and died July 29, 1947.

*Autopsy* showed diffuse involvement of the lungs, mediastinum, pericardium, pleura and pelvic organs by granulomatous tissue. The mesentery and omentum were also involved. The right lung was almost completely replaced by granulomatous tissue. The heart was small and showed invasion of the right atrium. The liver and spleen showed focal involvement. The inferior vena cava was obstructed by granulomatous tissue. Microscopic examination showed Hodgkin's disease. There was considerable variation in histologic structure ranging from granulomatous to sarcomatoid lesions.

*Comment.* This patient, with a severe form of Hodgkin's disease, became worse after Roentgen-ray therapy was started. Diffuse enlargement of the peripheral glands, absent before treatment, became a prominent feature after the first course of Roentgen rays was completed. Nitrogen mustard produced temporary remissions and a dissolution of the enlarged glands.

*Leukemia.* Six patients with lymphatic leukemia were treated with nitrogen mustard: 5 had the chronic type and 1 the acute type of the disease.

Four of the 6 were previously treated with Roentgen rays. In 3 patients remissions were produced varying from 6 weeks to 7 months in duration. The response was good in 1 and fair in 2 patients. One patient with chronic lymphatic leukemia remains in a remission of 7 months after one course of nitrogen mustard. Two other patients with the same type of disease obtained remissions of 6 weeks to 3 months. These 2 patients did not respond to a second course and died within 4 to 6 months after nitrogen mustard was begun. Two patients with the chronic type and 1 with the acute type of lymphatic leukemia did not respond to nitrogen mustard.

Five patients with chronic myelogenous leukemia received nitrogen mustard therapy. Three of these were previously treated with Roentgen rays: 1 patient also received radio-active phosphorous in addition to Roentgen rays. In 2 of the 5 the response was fair. One patient had a remission of 6 weeks and failed to respond to a second course of nitrogen mustard; this patient died 3 months after nitrogen mustard was begun. Another patient had a remission of 2 months following the initial course and remains in a remission 3 months following a second course of nitrogen mustard. Three patients with chronic myelogenous leukemia did not respond to nitrogen mustard.

*Lymphosarcoma:* Of the 5 patients with this disease treated with nitrogen mustard, all except one had previously had Roentgen-ray therapy. In 2 patients the response was good. One course of nitrogen mustard produced in these patients remissions of 3 to 5 months. The remissions consisted of a feeling of general well-being, a gain in weight, and a dissolution of the enlarged lymph glands. Three patients with lymphosarcoma did not respond to nitrogen mustard and died within 2 to 4 months after the drug was given.

*Carcinoma of the Lung:* Eleven patients with carcinoma of the lung were treated with nitrogen mustard. In 7 patients the pathological diagnosis was squamous cell carcinoma, in 4 patients it was anaplastic carcinoma. One patient (Case 37) with anaplastic carcinoma had considerable relief of a superior vena cava compression syndrome for 3 months from 1 course of nitrogen mustard. He did not respond to a second course of nitrogen mustard and died 5 months after the drug was given. Another patient (Case 31) with squamous cell carcinoma had relief of chest pain, cough and hemoptysis for 6 weeks following a course of nitrogen mustard. This patient died 7 months after nitrogen mustard was given. Nine patients with carcinoma of the lung did not respond to nitrogen mustard.

*Toxic Effects. Nausea and Vomiting:* This was present in most patients treated with nitrogen mustard. It usually occurred within 2 to 6 hours after an injection and lasted for 3 to 12 hours. Some patients had nausea or vomited only after the first injection. The nausea and vomiting were often followed by a temporary improvement in appetite. This was also noted in those patients who showed no significant response to nitrogen mustard. Preliminary sedation was effective in alleviating the nausea and vomiting in a number of patients.

*Venous Thrombosis:* Thrombosis of the vein at the site of the injection occurred in the majority of the patients treated with nitrogen mustard by the direct route. This complication was largely eliminated when the drug was injected into a rubber tubing during an infusion of normal saline.

*Hematological Effects:* Changes in the blood were usually evident during the week following nitrogen mustard therapy. These consisted of a drop in

the white blood cells associated with a reduction in the number of lymphocytes and granulocytes. A reduction in the number of platelets was also common. These changes usually lasted for 2 to 3 weeks. Leukopenic levels of 1000 white blood cells or less were noted in 4 patients and thrombocytopenia of 60,000 or less was found in 3 patients. Agranulocytosis and bleeding tendencies were not encountered. A slight reduction in the number of red cells and in the amount of hemoglobin was noted in a few patients. In some cases of Hodgkin's disease, an anemia that was present before treatment improved following a course of nitrogen mustard.

*Summary and Conclusions.* A group of 40 patients (Hodgkin's disease, 13 cases; leukemia, 11 cases; lymphosarcoma, 5 cases; and carcinoma of the lung, 11 cases) was treated with methyl bis ( $\beta$  chloroethyl) amine hydrochloride. Most of them were treated in the late stages of the disease and had had previous Roentgen-ray therapy.

In patients with Hodgkin's disease remissions were produced from one or more courses of nitrogen mustard. Dramatic results were observed in a few patients who were Roentgen-ray resistant. In patients with lymphatic leukemia, myelogenous leukemia and lymphosarcoma the results were not so encouraging. Although remissions of 3 to 5 months were observed in a few patients, the majority of the patients who showed a response were dead within 7 months after nitrogen mustard was first given. Nitrogen mustard did not appear to be of much value in the treatment of carcinoma of the lung.

The most important reaction to the use of this drug was its effect on the blood. This consisted of leukopenia, lymphopenia, granulocytopenia and thrombocytopenia. Recovery took place in 3 to 4 weeks. Instances of agranu-

locytosis and bleeding tendencies were value in Hodgkin's disease. Its use-not encountered. fulness in leukemia, lymphosarcoma,

From this study it is evident that and carcinoma of the lung remains to nitrogen mustard may be of particular be evaluated.

The author is indebted to Dr. A. J. Gitlitz, pathologist of the Greenville Hospital, and to Dr. A. M. Gnassi, pathologist of the Medical Center, Jersey City, New Jersey.

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# DEATH DURING SKIN TESTING

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SUDDEN death during diagnostic skin testing, it is believed, is sufficiently rare and disconcerting to warrant the report of another case. In our experience many physicians, who have not specialized in the practice of allergy, frequently employ diagnostic skin tests, and it is doubtful if many fully appreciate the hazards inherent in the procedure.

Anaphylactic shock and death in human beings has been reported from time to time, but the probability is that the number of such published reports inadequately reflects the real incidence of these episodes. Cook<sup>6</sup> in 1922 called attention to reports of violent reactions and sudden death that had been accumulated in the literature. Rosenau and Anderson<sup>20</sup> in 1906 reported 19 fatal cases; Gillette in 1909, 30 cases. Lamson<sup>16</sup> in 1924 reviewed the literature back to 1894, the year diphtheria antitoxin came into use. He found 41 incidences of anaphylactic death in human beings. Vaughan and Pipes<sup>29</sup> in 1936 added 22 cases, and Swineford<sup>21</sup> in 1946, 7 cases. It should be observed that the great majority of these accidents occurred in the course of once popular serum therapy and were attributable to sensitization to horse serum.

Death from skin testing has been previously reported, as far as we have been able to determine, only 10 times. In only 3 cases were autopsies performed. In 1922 Cooke<sup>6</sup> reported the death of a 3 year old asthmatic child,

occurring in 3 minutes after an intracutaneous test with 0.01 cc. of LePage Glue (0.1 mg. N/cc.). The symptoms were urticaria, edema, cough, dyspnea and cyanosis. In 1924 Lamson<sup>16</sup> reported the death in 2½ hours of a child with eczema after the injection intracutaneously of 0.05 cc. of egg white (0.15 mg. N/cc.) Cyanosis and edema characterized the episode. In 1928 Baagoe<sup>3</sup> reported death after sudden collapse in dyspnea of a patient who had received a test dose of 0.1 cc. of egg white. In 1929 Lamson<sup>17</sup> again reported the death of an asthmatic man, 34 years old, occurring 5 minutes after an intracutaneous test dose of 0.02 cc. of 1-500 buckwheat solution. The symptoms were cyanosis and dyspnea. In 1935 Freedman<sup>10</sup> reported the death of an asthmatic child 6 years of age, in 8 minutes after receiving 0.05 cc. of horse serum intracutaneously. The symptoms were urticaria, cyanosis and abdominal pain. In 1940 Ferguson<sup>9</sup> had a similar experience when 0.18 cc. of antitetanus serum was injected as a test intracutaneously into a 6 year old boy. Bloody mucous expectoration, dyspnea and urticaria preceded death 2 hours later. In 1942 Vance and Strassmann<sup>26</sup> reported the death of a 4 year old asthmatic girl with cyanosis, shock and coma occurring 3 minutes after skin testing with silk, wool and kapok. In 1943 Hunt<sup>14</sup> tested a 22 year old asthmatic woman with 0.2 cc. of guinea pig hemoglobin in saline. Death occurred in 10 min-

utes. Cyanosis and dyspnea were the symptoms. Wiseman and McCarthy-Brough<sup>32</sup> reported in 1945 the case of a 78 year old woman with life-long asthma who developed cough, dyspnea, cyanosis and coma and succumbed in 15 minutes after 17 intradermal tests in doses not greater than 0.02 cc. Six years before this she had been tested with similar extracts without untoward effects. Swineford in 1946<sup>21</sup> reported a case of a 49 year old woman with asthma who died 15 minutes after the onset of apprehension, cyanosis and dyspnea in the course of multiple skin testing. The offending antigen was not discovered.

**Case Report.** Mrs. Z. V. M., a white woman, aged 57, was referred for allergic study on account of asthma which she had had perennially with fall exacerbations since onset in 1914. At that time she was living in a damp mining town. In Mexico, where she next lived from 1924 to 1938 at an altitude of 6,500 feet, she had very few symptoms. She was especially free in the dry season. In 1938 she moved to Texas where her symptoms returned and were considerably worse. For the last 3 months (October, November, December, 1946) she had lived in Richmond, Virginia, where her attacks had become increasingly severe. She had been twice skin tested; the last time in June, 1945, in Nashville, Tennessee, where she gave strong reactions to cat hair, chicken and duck feathers, house dust and Bermuda grass. A number of other tests were said to have been negative. In 1933 the basal metabolic rate was said to have been minus 9. In 1943 and again in 1946 electrocardiographic tracings were reported as normal. Her father had had hay fever and migraine; a paternal grandfather, hay fever, asthma and migraine. As a child she herself had had frequent head colds and attacks of urticaria. She later developed symptoms suggestive of migraine. She reported that her attacks of asthma responded well to pyribenzamine orally and to aminophyllin intravenously, but she was violently opposed to the use of adrenalin, stating that it had produced immediate and alarming symptoms whenever given.

Physical examination revealed a well-nourished gray-haired woman, 5 feet 4 inches

tall, weighing 136 pounds, with a temperature of 98° F., pulse 82, and blood pressure 170/118. She was in no distress. The heart appeared normal, and aside from congestion of the nasal mucous membrane and diffuse wheezes throughout both lung fields, nothing of significance was made out. The urine was normal. Her hemoglobin was 16.3 gm., red blood cell count 4,930,000, and white blood cell count 8,400, with 67% polymorphonuclear leukocytes and 12% eosinophils. The sedimentation rate was 14 mm. in 60 minutes. Nasal blowings contained 5% eosinophils.

Preliminary scratch tests on the arms to groups of trees, grasses, weeds and flowers and to cottonseed, flaxseed, condiments, fish, mollusks, and egg were all negative. Intracutaneous tests, using the back, were then begun to the common foods, to cat, dog and cattle hair, and to chicken and duck feathers.<sup>o</sup> Fifty-six skin tests had been completed without any positive reactions, when she suddenly complained of air hunger and sat up to get her breath. Seen immediately by a physician, her expression was anxious, and she was moderately cyanosed. She was obviously having great difficulty getting her breath. Wheezing respiration was heard over the whole chest and the heart sounds were plainly audible. She was given 0.5 cc. of epinephrine intramuscularly without effect, followed by a hypodermic of 1/6 grain of morphine. She died 15 minutes after the onset of symptoms. In the excitement incident to this unexpected reaction, no attempt was made to read the skin tests finally, but the impression was that none of them had been positive.

An autopsy, performed 2 hours after death, was limited to the thorax and to the examination of the liver. Both chest cavities were filled by strikingly voluminous lungs. The left lung was bound to the thoracic wall by cobweb adhesions. The right lung was firmly adherent to the posterior wall of the thorax and to the dome of the diaphragm. When removed, both lungs failed to collapse, floated high in water, were pale, and markedly emphysematous. There were no large blebs on their surfaces. There were numerous small subpleural hemorrhages over the right lower lobe. There were submucous hemorrhages in the trachea which was pale and free of swelling or secretion. The same appearance was observed in the primary and secondary bronchi. No mucous plugs were seen. The heart was normal and contracted. All the cavities except the right auricle were devoid of blood. Sections of the lung showed hyaline thickening of the basement mem-

<sup>o</sup>All extracts were made by an experienced technician by the method described by Vaughan<sup>27</sup> (p. 272).

brane, round cell and eosinophilic leukocytic infiltration and edema of the walls of the secondary bronchi. The infolding of the mucous membrane of the bronchi was striking and strongly suggestive of spasm as an occluding factor. Marked mucin-secreting activity of the cells of the mucous membrane of the bronchi as well as of the mucous glands was observed. The lumens of the bronchi were partly filled with mucin. Less marked changes were observed in the smaller bronchi. Emphysema was striking. The trachea showed edema. The myocardium was normal.

**Discussion.** The course of events in this case raises several controversial questions. The first involves the relative advantage and risk of multiple, one-sitting skin tests as against what is perhaps commoner, the method of serial testing with a limited number of allergens at a time. Pratt in 1938,<sup>18</sup> from guinea pig experiments, concluded that "when either of 2 antigens alone is capable of producing moderate anaphylactic shock in specifically sensitized guinea pigs, the sum of these antigens in a single dose does not enhance the degree of shock, whereas doubling the shocking dose of either antigen alone results in an increased response." Waldbott<sup>30</sup> at the same time observed: "200 or 300 skin tests are often given at one sitting and only rarely do constitutional reactions occur, in spite of the fact that many skin tests may be positive. If there was an accumulative effect of antigens, we would encounter constitutional reactions on skin testing much more frequently." Swineford in 1941<sup>22</sup> quoted the above and condensed his findings in the conclusion that: "no evidence has been found in the literature to support the statements that routine multiple skin testing is more dangerous than a few tests at one sitting."

On the other hand it has long been a clinical dictum that sensitive individuals exposed to one antigen are much more apt to exhibit symptoms if subjected simultaneously to another

antigen to which they are also sensitive. Thus a ragweed-cat-sensitive child may be free of symptoms in August if the cat is sent away, and may play with the cat with impunity during other months of the year. But to play with the cat in August is a sure way of precipitating an asthmatic attack. In 1922 Cooke,<sup>6</sup> although unable to prove it, thought that a reaction to multiple skin testing was "more likely to ensue as a result of the sum total effect of all the allergens exerting their influence upon the same reacting mechanism." It is not unusual during skin testing for a single massive reaction to herald a severe constitutional reaction. But this is not always the case. A reaction so severe as to cause death in a few minutes, as in the case reported, may give no warning in the degree of reactivity. Gay<sup>11</sup> has observed that "skin reactions and constitutional behavior do not necessarily parallel one another."

Can epinephrine, a drug so feared by the patient on account of previous distressing symptoms, have had anything to do with the results? Deissler<sup>27</sup> has described a case sensitized to epinephrine. Occasionally hypersensitivity followed by major accidents has resulted from the use of epinephrine. Sudden death has resulted from the injection of 1 cc. of a 1-1,000 solution.<sup>8</sup>

Can the employment of morphine in this case have contributed to the end result? There is opposition among allergists as a group to the use of morphine in the treatment of asthma. A drug which depresses the respiratory center and stimulates bronchial spasm, however slight, has been regarded as a possible determining factor in many cases of fatal asthma. But reference to the literature of allergy on the use of morphine in asthma leaves the average physician in somewhat of a quandary. One group of authors unequivocally



condemns it.<sup>4,12,23,25,28</sup> Another recommends its use with reservations.<sup>1,19,24</sup> While still a third group supports its use, Coke<sup>2</sup> advising that "The next step to take in cases in which adrenalin is without effect is to give an injection of morphine. I think it is important to give enough morphine." In Walzer's opinion "morphine is a valuable drug for controlling a severe asthmatic paroxysm."<sup>31</sup> Cooke summarily dismisses the question stating that "There are many who believe that opium and its derivatives should never be used in asthma. I do not concur."<sup>7</sup> The employment of morphine in our case was a mistake. Our own opinion is emphatically against its use in the treatment of asthma of any type.

The employment of the back in preference to the arms as a test site raises also the question of relative risk. In case of a constitutional reaction, a tourniquet can be applied to the extremity, if the arm has been used, and should reduce or delay the absorption into the general circulation of a toxic substance injected into the skin distal to the point of application. On the other hand, it is our belief that by the time a tourniquet can be applied, an irreversible train of circumstances has often been set in motion. After all, our chief reliance in cases of constitutional reaction is in epinephrine. The back is favored because of convenience. It offers a large area for testing so that test sites need not be crowded. Injections are less painful and the skin of this region as shown by Alexander and McConnell<sup>2</sup> is more reactive than the arm. This does not imply that constitutional reactions are more apt to arise from such injection sites. There are too many factors to be taken into consideration to speak dogmatically. When the arms are used for preliminary scratch tests, we believe that the employment of the back for intracutaneous testing

is reasonably safe. By this method we have performed thousands of skin tests with very few systemic reactions.

What was the mechanism of death in this case? It is not enough to say that the patient died of asphyxia resulting from bronchial obstruction. The usual answer is that edema of the walls of the small bronchi, plus smooth muscle spasm, plus mucous plugging of the lumens of the bronchi in varying combinations produces the obstruction. Edema is so fundamental to human allergy, and can develop so rapidly as in cases of generalized urticaria, that this factor, plus the mucous plugs which are easy to demonstrate after death, is usually regarded as a primary cause of fatal bronchial obstruction. On the other hand, bronchial spasm is easily demonstrated as the essential factor in death in guinea pig anaphylaxis. Huber and Koessler<sup>13</sup> made numerous micro measurements and appear to have shown hypertrophy of bronchial smooth muscle in asthmatic subjects. Klemperer<sup>15</sup> reminds us that hyperactivity of smooth muscle is also fundamental to the allergic reaction and need not be associated with any obvious morphological lesion, maintaining that "the gross anatomy of bronchial asthma shows only the result of the spasm of the small bronchioles." In the case reported here, as one viewed the lungs in the gross and studied the sections under the microscope, direct evidence of spasm or of extensive edema was lacking, unless one is willing to accept the infolding of the mucous membrane as indicating smooth muscle contraction of the bronchial walls. Mucus in the lumens of the small bronchi was impressive, but aside from this the cause of obstruction remained a matter of conjecture.

Summary. A case of death with autopsy is reported occurring in the course of routine skin tests in a woman

who had been safely skin tested on 2 previous occasions. Death was without the warning of at least one massive skin reaction and occurred 15 minutes after the onset of symptoms. Neither edema nor urticaria was manifest and death

was thought to be the result of asphyxia from bronchial obstruction. The effect of multiple intracutaneous skin tests applied to the back and the possible influence of epinephrine sensitivity and of morphine have been considered.

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# STUDIES IN THE RELATION OF THE HEMOLYTIC STREPTOCOCCUS TO RHEUMATIC FEVER INFECTION, AND OTHERS\*†

## V. STREPTOCOCCAL ANTI-HYALURONIDASE (MUCIN-CLOT-PREVENTION) TITERS IN THE SERA OF PATIENTS WITH RHEUMATIC FEVER, STREPTOCOCCAL

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THE etiology of rheumatic fever is at present unknown. Of the recorded clinical and experimental studies of this disease 2 categories of observations, the epidemiologic<sup>15</sup> and immunologic,<sup>5</sup> have yielded suggestive evidence of a possible specific etiologic agent, in both cases the hemolytic streptococcus. However, extensive investigations of the relation between this organism and rheumatic fever have failed to point to any constituent or product of the streptococcus which might be the immediate cause of the phenomena of rheumatic fever, or to any mechanism by which such an agent could exert its effects.

As part of a systematic investigation in these laboratories<sup>6,7</sup> of the relation between the hemolytic streptococcus and rheumatic fever, a biologic property of the hemolytic streptococcus which must be considered is the production of hyaluronidase. This aspect of the investigation has especial current interest because the possible role of streptococcal hyaluronidase in the pathogenesis of rheumatic fever has been the subject of some recent speculation.<sup>14</sup> The basis for this speculation lies in the facts that rheumatic fever is a disease of hyaline connective

tissue, that hyaluronic acid, which characterizes hyalin, is depolymerized by hyaluronidase,<sup>12</sup> and that the hemolytic streptococcus is one of the bacterial species which produces this enzyme.<sup>13</sup>

The effect of streptococcal hyaluronidase as a spreading factor in the tissues of rheumatic subjects has been studied elsewhere.<sup>8</sup> In this investigation antibodies to this enzyme have been measured in such patients. Of the methods available for measuring this enzyme *in vitro* the mucin-clot-prevention (M.C.P.) test<sup>17</sup> was used. This test is one of three available physico-chemical tests for the activity of hyaluronidase the others being the turbidimetric and viscosimetric, respectively. The reason for the choice of the M. C. P. test and the possible differences among the tests are presented elsewhere.<sup>1</sup> This method has been used for measuring antibodies to clostridial<sup>11</sup> and streptococcal hyaluronidase. In the latter case, Friou and Wenner<sup>2</sup> have shown that many normal human sera contain neutralizing substances for streptococcal hyaluronidase. Using an index which compares the amount of enzyme neutralized by constant amounts of experimental sera, these

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authors found that of 21 rheumatic patients, 20 showed indices of neutralization higher than was normal for that age-group. These inhibition ratios were not strikingly different from those found in convalescents from streptococcal infections.

**Methods and Materials.** *Hyaluronic Acid.* In various stages of the preparation and use of this reagent it may be in the form of hyaluronic acid or of potassium hyaluronate, but for simplification of nomenclature we shall make all references to it as hyaluronic acid. The method used for preparing this substrate was adapted from that of McClean, *et al.*<sup>11</sup> Three modifications of the method they described were found to be advantageous: (1) The suspension of minced umbilical cord was treated in the Waring blender at each extraction, with a resultant marked increase in yield of hyaluronic acid; (2) the solution of crude hyaluronate was poured into the alcohol-potassium acetate solution, rather than vice versa. In addition to a better precipitation of the hyaluronic acid an important advantage of this modification is the fact that 95% ethyl alcohol may be substituted for absolute alcohol under these circumstances; (3) the clot of hyaluronic acid was minced with scissors and allowed to dry in air, in a shallow horizontal layer from which the ether was removed by suction.

The hyaluronic acid, as prepared in this way, was white or tan in color and could be redissolved with ease for testing. The average yield was approximately 0.9% of the weight of umbilical cords as stored in acetone.

*Hyaluronidase.* Streptococcal hyaluronidase was prepared from a suitable strain of group A hemolytic streptococcus, H<sub>11</sub>, which was supplied through the courtesy of Dr. Karl Meyer. It was found that the culture supernate afforded an abundant and simple source of the enzyme, so that this was used as starting material, rather than extracts of whole streptococci. The hyaluronidase-containing material was prepared as follows: Three liters of dextrose broth (Difco) or of a protein-free medium described elsewhere,<sup>10</sup> were seed-

ed with 300 cc. of a 6 hour seed culture. After 18 hours of incubation the culture medium in which the streptococci had grown was freed of the organism by centrifugation and concentrated approximately 10 fold by pervaporation overnight. The concentrated medium was then freed of residual streptococci by centrifugation at 5000 R.P.M. for 30 minutes and dialyzed overnight against running tap water. After final dialysis against distilled water the preparation was desiccated from the frozen state and stored at -10° C., not *in vacuo*. It was found that the potency of the preparation remained unchanged for many months.

Pneumococcal and clostridial hyaluronidase were prepared in a similar way. In the latter case thioglycollate medium was used rather than dextrose broth. Testicular hyaluronidase was prepared according to the method of Madinaveitia.<sup>10</sup>

*Hyaluronidase and Anti-hyaluronidase Tests.* These tests were performed, with minor modifications, according to the technic of McClean, *et al.*<sup>11</sup> The relative volumes of the reagents in the anti-hyaluronidase test were suggested by technical factors, and by the desirability of making the serum dilutions generally similar to those used in other serologic tests of the same sera in progress at the time. The volumes of reagents in the hyaluronidase tests were in turn adjusted to reach the same total volume as the reagents in the anti-hyaluronidase test, since the former was essentially used in calibrating the neutralization test.

In the hyaluronidase test, 0.2 cc. of a solution of the hyaluronidase preparation dissolved in physiologic saline solution was incubated with an equal volume of a solution of potassium hyaluronate. The latter contained 2 mg. of hyaluronic acid per cc. in distilled water, with one-sixteenth volume of normal horse serum added. An additional 0.4 cc. of physiologic saline solution was present in each tube. As soon as the enzyme had been added to the substrate, the tubes were incubated at 37° C. for 20 minutes. At the end of that period the tubes were quickly transferred to an ice-water bath. After 5 minutes of chilling, 0.2 cc. of 2 N acetic acid was added to each tube. The

racks were shaken vigorously and the clots were read. The appearance of a flocculent precipitate was taken as evidence of essentially complete digestion of the hyaluronic acid, a small but single fibrous clot was taken as evidence of partial digestion, and a mucin clot fully as large as that in control tubes without hyaluronidase was considered negative for hyaluronidase activity.

In the anti-hyaluronidase test the enzyme was used in 3 times the amount which caused partial digestion of the hyaluronate, or twice the amount which caused almost complete digestion. The use of a smaller number of units of enzyme in the neutralization tests was found to cause ragged clots and poorly defined end-points. The successive 2 fold dilutions of serum, in volume of 0.4 cc. were incubated for 20 minutes at room temperature with 0.2 cc. of the solution of hyaluronidase. The concentration of the latter had been adjusted, on the basis of preliminary hyaluronidase tests, so that 0.2 cc. contained 3 units as defined above. The hyaluronate-horse serum solution was now added as in the case of the hyaluronidase test described, and the test was completed in the same way. The initial dilution of serum corresponding to the last tube which showed a full clot was considered the titer of the serum. If this tube was succeeded by one in which there was a smaller mucin clot, rather than a flocculent precipitate, indicating partial neutralization, the titer was considered to be half a 2 fold step higher.

*The Preparation of Sera.* The sera of newborn infants were prepared from blood collected from the umbilical cords in the delivery rooms of the Philadelphia General Hospital. The sera of older infants were collected in the wards and outpatient department of The Children's Hospital of Philadelphia. These infants ranged in age from 6 months to 3 years. The sera representing the antibody levels in normal children were collected at The Children's Hospital of Philadelphia, and in local private schools. The sera of young adults were collected at the Student Health Service of the University of Pennsylvania, and in the Maternity Wards of the Philadelphia General Hospital.

For the study of the anti-hyaluronidase titer in acute streptococcal disease, blood specimens were collected from children with scarlet fever at the Philadelphia Hospital for Contagious Diseases, during the first half-week and during the third week of the disease. These patients were not treated with sulfonamides. In a number of these cases, additional specimens were drawn 3 weeks or 4 months later.

In the case of rheumatic patients the blood specimens were drawn at weekly, bi-weekly, or monthly intervals, depending on the severity of the rheumatic process, in correlation with the clinical studies to be described below.

Blood specimens were collected with a minimum of sodium citrate as anticoagulant, in order to allow for the determination of the erythrocyte sedimentation rate, white blood count, and concentration of hemoglobin. The plasma was drawn off each blood specimen and frozen as soon as the tests above had been completed. When a specimen was to be tested, it was thawed, cleared by centrifugation of the fibrinogen which had precipitated on freezing, and diluted for the test. A single dilution of 1:8 or 1:16 was made of each serum, in comparative estimations of anti-hyaluronidase and antibodies to other streptococcal antigens.

*The Study of the Patients and the Criteria of Activity of the Rheumatic Process.* The rheumatic patients were studied in acute, convalescent and quiescent stages of the disease in the institutions from which this work is reported. The patients were examined at least every 2 weeks while in the acute or convalescent wards and at each visit to the clinics. These examinations included the following: *symptoms*—anorexia, headache, precordial, abdominal or arthritic pain, cough, dyspnea, and epistaxis; *physical signs*—cardiac rate and rhythm, distance of apex beat from the midline, murmurs, with distance of transmission of each, and other adventitious sounds, palpable thrills and friction rubs, hepatic enlargement and edema, rashes, subcutaneous nodules and chorea. Laboratory examinations included the erythrocyte sedimentation rate, white blood cell count and hemoglobin concentration. The vital capacity was usually

determined at bi-weekly intervals, and electrocardiograms were taken as required. The erythrocyte sedimentation rate was done by a method described elsewhere.<sup>4</sup> It involved a series of readings of the erythrocyte level at 5-minute intervals, in order to determine the rate of free fall of the corpuscles, and a correction for the relative volume of erythrocytes.

The patients selected for serologic study were, of course, only those in whom the diagnosis of active rheumatic fever was beyond doubt. All the children who are referred to in this paper as active rheumatics had active carditis.

The amount of hyaluronic acid was now kept constant at a level (0.4 mg. in 0.2 cc.) which would give an easily discernible and substantial clot (half that amount barely sufficed to produce a small mucin clot) and the concentrations of enzyme and serum were varied simultaneously, in order to ascertain the relationship between these two reagents. The results of such an experiment, as seen in Table 2, show that an inverse proportion exists between the amount of enzyme used, and the dilution of serum which suffices

TABLE 1. QUANTITATIVE RELATIONS BETWEEN HYALURONIDASE AND HYALURONIC ACID

<i>Hyaluronidase</i>	<i>Hyaluronic Acid, mg.</i>				
<i>mg./cc.</i>	0.8	0.6	0.4	0.3	0.2
0.18	1	0	0	0	0
0.13	1	0	0	0	0
0.09	2	1	0	0	0
0.06	2	2	±	0	0
0.04	2	2	1	0	0
0.03	2	2	2	±	0
0.02	2	2	2	1	±
0	2	2	2	2	±

2 = full mucin clot (of native hyaluronic acid)

1 = smaller clot

± = shreds of clot

0 = amorphous precipitate (of depolymerized hyaluronic acid)

**Results.** *Quantitative Relations among Substrate, Enzyme, and Neutralizing Antibody.* Preliminary experiments were carried out on the quantitative relations of the reagents. The relation between concentrations of hyaluronidase and hyaluronic acid was investigated by allowing various quantities of the enzyme to act on different amounts of the substrate. The results of a typical experiment of this sort are shown in Table 1.

The data in Table 1 show essentially a direct proportion between the amount of hyaluronic acid present in the tube and the amount of hyaluronidase required to digest it over the narrow range in which this test was practicable. Similar results were obtained by McClean<sup>11</sup> in the case of testicular hyaluronidase.

to neutralize it. The end points thus fall in a straight line, inclined at 45°, which is characteristic of *in vitro* immunologic neutralizations. In the rows which represent the smallest amounts of the enzyme, it is seen that the end point of neutralization is indistinct. For this reason the amount of hyaluronidase used in the mass serologic tests was that corresponding to row C in this experiment.

*Reliability of Measurements of Hyaluronidase by the Mucin-Clot Prevention Test, by Comparison with Spreading Potency in the Skin.* It was mentioned above that of the 3 available *in vitro* tests for hyaluronidase the M.C.P. test was chosen because it was more suitable for adaptation to this study. It was therefore thought advisable to confirm the reliability of this

test. An opportunity to compare the M.C.P. test, as done in the work here reported, with the spreading test was afforded by work done on purification and sterilization of streptococcal hyaluronidase reported elsewhere.<sup>8</sup> Preparations of hyaluronidase which had been examined for spreading potency in the rabbit's skin were titrated for hyaluronidase by the M.C.P. test. Results of such tests are given in Table 3. The Table shows that the M. C. P. titration of hyaluronidase preparations agrees well with the titration of the same material by actual spreading effect in the skin.

of hyaluronidase or hyaluronic acid. In order to test the specificity of the reaction, parallel anti-hyaluronidase tests were done versus testicular, pneumococcal and clostridial hyaluronidase. Each of the other enzymes was, of course, present in the same number of units of potency as the streptococcal hyaluronidase.

Table 4 gives the results of such tests. These data show that the human sera tested did not interfere with the digestion of hyaluronic acid by clostridial or testicular hyaluronidase. Some of these sera did neutralize pneumococcal hyaluronidase, but in a much lower

TABLE 2. QUANTITATIVE RELATIONS BETWEEN STREPTOCOCCAL HYALURONIDASE AND ITS NEUTRALIZING ANTIBODY

<i>Hyaluronidase</i>		<i>Dilution of Serum 5507</i>								
		1:64	1:128	1:256	1:512	1:1024	1:2048	1:4096	1:8192	
	<i>mg./cc.</i>									
A	0.5	2	2	0	0	0	0	0	0	0
B	0.25	2	2	1	0	0	0	0	0	0
C	0.125	2	2	2	1	0	0	0	0	0
D	0.063	2	2	2	2	1	±	0	0	0
E	0.031	2	2	2	2	2	1	1	±	0
F	0.016	2	2	2	2	2	2	2	2	0

2 = full mucin clot (of native hyaluronic acid)

1 = smaller clot

± = shreds of clot

0 = amorphous precipitate (of depolymerized hyaluronic acid)

*The Serologic Specificity of the Neutralizing Antibodies to Streptococcal Hyaluronidase in Sera of Human Subjects.* In initial exploratory work a miscellaneous group of sera from apparently normal subjects was tested for the presence and concentration of neutralizing substances for streptococcal hyaluronidase (anti-hyaluronidase). It was found that measurable amounts of such neutralizing substances were present in almost every serum tested, in titers varying over a wide range. The same observation has since then been reported by others,<sup>2</sup> as noted above.

These data did not indicate whether we were observing the effect of a specific neutralizing antibody or of some constituent of serum which might interfere with the biochemical action

range of titers than in the case of the streptococcal enzyme. There was, moreover, no correlation between anti-pneumococcal and anti-streptococcal titers.

Recent studies in collaboration with Dr. Dan H. Moore indicate that the neutralizing antibody to streptococcal hyaluronidase is in the gamma globulin fraction of electrophoretically separated serum.

*The Titer of Antibodies to Streptococcal Hyaluronidase in Normal Individuals of Various Age-Groups.* As a preliminary to the study of these antibodies in streptococcal and rheumatic infection it was necessary to study the titers found in the presumably normal population. These determinations included those on sera of 94

neonatal infants, 118 older infants (6 months to 3 years of age), 185 children (4 years to 15 years of age) and 135 young adults.

The results of these determinations are shown in a percentage-frequency chart in Fig. 1. It can be seen in the Figure that antibodies to streptococcal hyaluronidase were found among all age-groups. Among the infants most sera were found to contain no measurable amount of neutralizing antibody to streptococcal hyaluronidase.

reflected completely the pattern of their mothers, who were included among the young adults.

*Antibodies to Streptococcal Hyaluronidase in Scarlet Fever.* In order to observe the effect of acute infection by the hemolytic streptococcus on the titer of this antibody, sera were obtained from children with acute scarlet fever (within the first 5 days after the onset of symptoms) and at the end of the 3rd week of the disease. Of the 130 such pairs of sera collected, 34

TABLE 3. COMPARISON OF THE MUCIN-CLOT-PREVENTION TEST FOR HYALURONIDASE WITH SPREADING POTENCY

Material	Spreading potency, Minimal effective dose	Assay of Hyaluronidase In Vivo and In Vitro						
		Results of M.C.P. Test						
		Mg./cc. of enzyme preparation						
		0.25	0.125	.06	.03	.015	.008	.004
	mg.							
CS 119 Original	.006	0	0	0	±	1	2	2
CS 119 partially purified	.003	0	0	0	0	0	1	2
CS 119 partially purified, irradiated	.006	0	0	0	0	1	2	2
CS 119 partially purified, glass-filtered	.012	0	0	0	1	2	2	2
CS 119 partially purified, Seitz-filtered	.048	0	1	2	2	2	2	2

2 = full mucin clot (of native hyaluronic acid)

1 = smaller clot

± = shreds of clot

0 = amorphous precipitate (of depolymerized hyaluronic acid)

The antibody titers of the remaining infants were low and the majority fell in the range between 8 and 16. The sera of children of slightly older age showed more antibody to streptococcal hyaluronidase. There were fewer sera with no measurable antibody. The range of titers was distinctly wider, the greatest aggregation of titers appearing between 8 and 128. The sera of young adults were grouped about a mean titer of 32, with 65% falling between 16 and 64. Neonatal infants

were followed by a third specimen which was obtained either 3 weeks or 4 months after recovery from the acute illness. The percentage-frequency charts of titers found in the same children at the onset of scarlet fever and 3 weeks thereafter are shown in Fig. 2. These charts show that the titers are generally higher as a result of the streptococcal infection. The mean anti-hyaluronidase titer found during the 3rd week of the disease was 73, in comparison with the geometric mean titer\*

\* The geometric mean titer is obtained by noting the logarithms of the individual titers to the base 2 (since the dilutions are made in 2-fold steps). The average of these logarithms is then computed, and the antilogarithm of this average is the geometric mean. This procedure is necessary because the conventional dilutions of sera in such tests result in a geometric series of decreasing concentrations, and because of the characteristic distribution of antibody titers in human groups.



of 20 which had been found at the onset of the disease. Of the individual pairs tested, 45% showed no significant increase in titer, 22% a 2-fold rise, and 33% a 4-fold or greater rise.

Anti-hyaluronidase titers were observed 6 weeks after the onset of the acute episode of scarlet fever in 15 children. When these were compared with those of the same children during the 3rd week of the disease it was

*Anti-Hyaluronidase Titers in Acute and Quiescent Rheumatic Fever.* Neutralizing antibodies to streptococcal hyaluronidase were measured in the sera of 135 patients with quiescent rheumatic disease. The range of titers found, from less than 8 to 256, was similar to that found in the normal children of comparable age, and the geometric mean titer was 52.

Among 100 children with active rheu-

TABLE 4. SPECIFICITY OF NEUTRALIZING ANTIBODIES TO STREPTOCOCCAL HYALURONIDASE

Source of Serum	Titer of Neutralization of Hyaluronidase			
	Streptococcal	Pneumococcal	Clostridial	Testicular
Normal child	32	—	—	—
Normal child	64	—	—	—
Normal child	8	12	—	—
Normal child	18	6	—	—
Normal child	128	—	—	—
Normal youth	48	—	—	—
Normal youth	24	8	—	—
Normal youth	32	—	—	—
Normal youth	96	—	—	—
Quiescent rheumatic	64	—	—	—
Quiescent rheumatic	192	—	—	—
Quiescent rheumatic	96	—	—	—
Quiescent rheumatic	96	6	—	—
Convalescent from scarlet fever	384	—	—	—
Convalescent from scarlet fever	768	—	—	—
Convalescent from scarlet fever	512	8	—	—
Convalescent from scarlet fever	256	12	—	—
Acute rheumatic	1024	—	—	—
Acute rheumatic	768	—	—	—
Acute rheumatic	2048	—	—	—
Acute rheumatic	512	—	—	—
Acute rheumatic	512	6	—	—
Acute rheumatic	2048	—	—	—
Acute rheumatic	1024	6	—	—

— = less than 4

found that in somewhat more than half, the titer had not changed significantly from the time of clinical convalescence to 3 weeks thereafter. Most of the others showed a slight increase in titer. The mean titer of this group was 120.

Of the patients whose serum specimens were obtained 4 months after acute scarlet fever 88% showed anti-hyaluronidase titers which were at least as high as at the height of the disease.

matic carditis the anti-hyaluronidase titers were found to be much higher. The range of titers, except for 3 values of 32, was from 128 to 4096, with a geometric mean titer of 580. These distributions are shown in Fig. 2. This Figure shows also that the anti-hyaluronidase titers in acute rheumatic fever were higher than those following scarlet fever.

*Anti-Streptococcal - Hyaluronidase*

*Titers during Fluctuations in the Severity of the Rheumatic Process.* Almost all the patients in the acute rheumatic group were followed for considerable periods of time. Among patients who showed continued activity of the rheumatic process of constant or fulminating severity, the anti-hyaluronidase titer remained elevated. The majority of patients studied were observed during a single episode of the disease, with a decline in the acuity of the illness to quiescence. In these patients it was found that the anti-hyaluronidase titer did not decline with

the clinical severity of the disease, but remained in the same range for a considerable period of time after the rheumatic infection had become quiescent. The fall in concentration of these antibodies was noted in many of these patients some months thereafter.

Finally, some of the patients showed a polycyclic course, so that it was possible to observe the correlation in a given patient between the clinical activity of the rheumatic disease and the serum titer of anti-hyaluronidase.

In the case of patients whose rheumatic process had been quiescent for

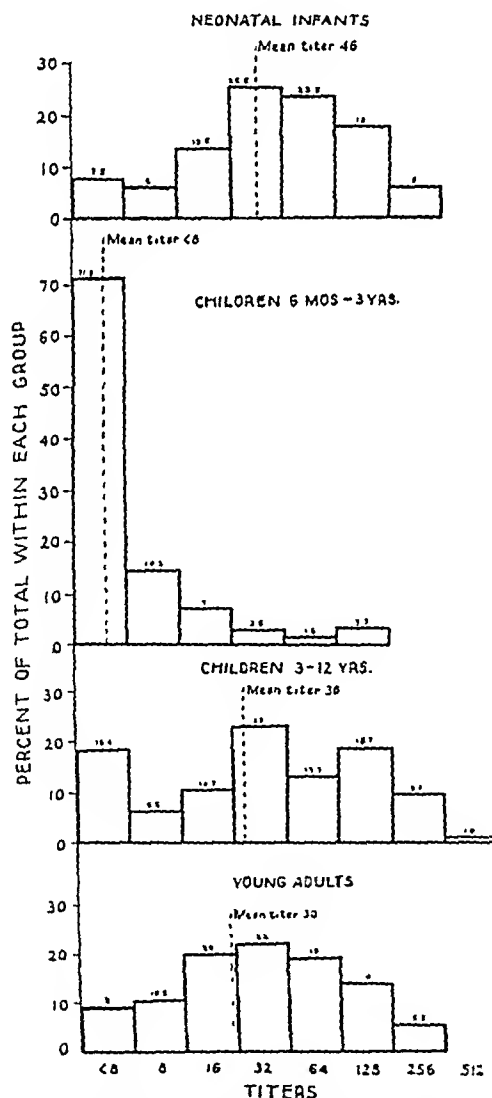


Fig. 1.—The frequency distribution, in percentage, of streptococcal anti-hyaluronidase titers in normal subjects of various age-groups. The percentages are given by the small numbers at the head of each column.

some time, so that the anti-hyaluronidase titer had declined from the original elevated value, the titer of this antibody rose again at the time of the rheumatic recrudescence. Smaller fluctuations of the activity of the rheumatic process, or rheumatic recrudescences not separated by considerable intervals of time, however, were not accompanied by definite changes in anti-hyaluronidase titer. Clinical details of the study of variations in rheumatic activity in correlation with the anti-hyaluronidase titer will be presented elsewhere.<sup>3</sup>

**Discussion.** *The Mucin-Clot Prevention Test as an In Vitro Measure of*

*Hyaluronidase.* As was stated above, the choice of the M.C.P. test for this work was made on the basis of adaptability to serologic analysis. Because of this, and because the precise chemical basis of the mucin clot reaction is not understood, it was advisable to test the reliability of this reaction. In all work on the measurement of hyaluronidase *in vitro*, the spreading potency in the skin has been used as the standard of comparison, since the latter affords a direct observation of the biologic phenomenon involved. The titration of spreading factor cannot be made in steps smaller than 2-fold, and within

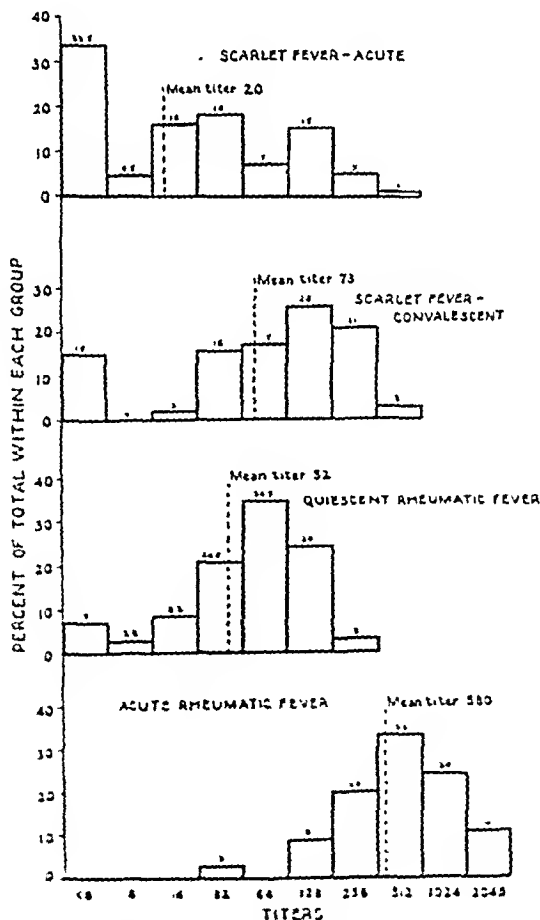


Fig. 2.—The frequency distribution, in percentage, of streptococcal anti-hyaluronidase titer in streptococcal infection and rheumatic fever.

this limitation excellent agreement was found in this study between spreading potency and the M.C.P. measure of hyaluronidase in various preparations incidental to purification and sterilization of the enzyme.

*The Occurrence of Neutralizing Antibodies for Streptococcal Hyaluronidase in the Normal Population.* This finding is of interest with regard to the production of hyaluronidase by hemolytic streptococci and with regard to the epidemiology of this organism.

Freshly isolated strains of group A hemolytic streptococci have been examined by several authors for production of hyaluronidase *in vitro*. Of several strains tested, detectable amounts of this enzyme were found only in strains of type 4 by Hobby, *et al.*<sup>9</sup> Crowley<sup>1</sup> found that only one additional type, type 22, of a total of 308 isolations of hemolytic streptococci, produced demonstrable hyaluronidase in culture. The finding of neutralizing antibodies to streptococcal hyaluronidase in almost all the tested sera derived from the presumably normal population past infancy must mean, however, as Friou and Wenner<sup>2</sup> have pointed out, that the enzyme is in fact produced by all or almost all strains of group A hemolytic streptococci, but often in such small quantities as to be detectable only indirectly, by means of the relatively large amounts of antibody to which minute amounts of the enzyme give rise. The circumstance which makes possible such detection is the broad reactivity of streptococcal hyaluronidase within group A.

The other implication of the widespread occurrence of anti-streptococcal-hyaluronidase in normal sera is also of epidemiologic interest, since this wide occurrence of the antibodies points to the ubiquitous character of the hemolytic streptococcus as an invader of the human upper respiratory tract, whether or not acute infection is present.

It is of some interest to compare the antibody titers to streptococcal and pneumococcal hyaluronidase. The latter antibody is met with such frequency that there can be little doubt that, as in the case of group A hemolytic streptococci, the enzyme is broadly reactive and is produced by the great majority of strains. The striking difference in range of neutralizing titers against enzymes of these two sources implies that although both streptococci and pneumococci are found in the normal and inflamed human throat, the streptococcus must be much more prevalent and effective as an invader of the human host.

The fact that no neutralizing effect could be found to testicular or clostridial hyaluronidase indicates that the anti-hyaluronidase effects measured involved true neutralization by antibodies, rather than non-specific interference by some constituent of serum with the enzymatic activity of hyaluronidase.

The occurrence of antibodies to streptococcal hyaluronidase in the population at large, and the rising range of titers with increasing age is, then, explained on the basis of 2 facts: broad reactivity of streptococcal hyaluronidase within the group of human pathogens, and the prevalence of contact between the streptococcus and the human host. A similar explanation was given for the widespread occurrence of complement-fixing antibodies to somatic fractions of the hemolytic streptococcus, described elsewhere.<sup>6</sup>

The range of titers in the normal children, and in acute streptococcal infection, is less uniform in the case of anti-hyaluronidase than in the case of antibodies to those fractions. This may well be due to the fact that the percentage content of each somatic fraction probably varies only slightly among strains of hemolytic streptococci, whereas the rate of production of the

enzyme may well vary over a range of several orders of magnitude. Thus the antigenic stimulus of the latter case may vary quite widely, with corresponding variations in the resulting titer of antibody. The same consideration would apply to the "booster" effect of subclinical contacts with the hemolytic streptococcus, which is responsible for the sustained elevation of anti-hyaluronidase titers after acute streptococcal or rheumatic infection.

*The Significance of Elevated Anti-Hyaluronidase Titers in Acute Rheumatic Fever.* The data presented here show unequivocally that the streptococcal anti-hyaluronidase titer is elevated in acute rheumatic fever. On comparing the titers found in acute and quiescent rheumatic fever, it was found that 84% of the values found in the acute group were 384 or more, and thus were higher than any found among the quiescent rheumatics. The geometric mean titers were 580 and 52, respectively. The anti-hyaluronidase level referred to, 384, was also higher than 98% of the presumably normal controls, whose geometric mean titer was 36. The data given certainly point to an extensive contact with the hemolytic streptococcus in the recent history of a patient with acute rheumatic fever, which is in agreement with almost all of the serologic work which has been done on this problem.

The comparison of the anti-hyaluronidase titers of acute rheumatic subjects with those of a group of convalescents from a frank streptococcal infection, scarlet fever, is, however, of some interest, for it is seen that the mean titer in active rheumatic fever is 5 times as high as it is following scarlet fever, with corresponding differences in the distribution of individual titers. The possibility was entertained that this difference might be due to a factor of time, inasmuch as patients

with acute rheumatic fever are in general seen for the first time a few weeks after the onset of any preceding streptococcal infection. Although 3 weeks is generally considered an adequate period for the attainment of maximal antibody response in acute infection, a longer effective period of antigenic stimulation in the case of streptococcal hyaluronidase would be consistent with the fact that the hemolytic streptococcus produces little hyaluronidase, in comparison with other metabolic products; so much so that direct search for the enzyme in culture media led to the impression that only a few strains of the organism produce the enzyme.<sup>1,9</sup> (This is in contradistinction to the hemolysin, which is readily found in streptococcal culture filtrates.)

In order to examine the validity of such an explanation, sera were collected from as many of the convalescents of scarlet fever as possible, after an additional interval of 3 weeks. A comparison of anti-hyaluronidase titers at this time, 6 weeks after the onset of the illness, with those taken at the time of convalescence showed that some of these children, slightly less than half, had higher titers at the 6th week than at the third. The mean antibody titer of these 6th-week specimens was 120 which, although higher than the mean of 73 in the 3rd week, was approximately one-fifth the mean titer found in acute rheumatic fever. In the 5th month after the onset of scarlet fever the mean anti-hyaluronidase titer had returned to the value which obtained in the 3rd week.

It is thus quite unlikely that the factor of time accounts for the difference between anti-hyaluronidase titers of convalescents from streptococcal infection and patients with acute rheumatic fever. Since no chemotherapy was given to the patients with scarlet fever it was not necessary to consider such a factor as a possible cause of the lower

range of titers in the convalescents from scarlet fever in comparison with the acute rheumatic group. Since work now in progress indicates that antibody levels to the other streptococcal antigens under investigation in these laboratories do not show such marked differences between the convalescents from scarlet fever and the acute rheumatics, this work raises the possibility that hyaluronidase, or strains or variants of streptococci producing unusual amounts of hyaluronidase, may be related in some way to the pathogenesis of rheumatic fever. The necessarily indirect method of investigating such a relationship—that of measuring antibodies to hyaluronidase rather than the enzyme itself—may represent a limitation in demonstrating an entirely clear-cut distinction with respect to hyaluronidase between patients with rheumatic fever and those with streptococcal infection. On the basis of the results reported it is impossible to say whether there exists a special relation of streptococcal hyaluronidase to rheumatic fever. Such a relation is, however, a possibility which cannot be excluded in the face of these data.

*Diagnostic Applications of the Streptococcal Anti-Hyaluronidase Test.* Aside from considerations of a possible role of anti-hyaluronidase in the pathogenesis of rheumatic fever, the question arises of its usefulness in the laboratory diagnosis of rheumatic fever. This test suffers the same shortcoming in this regard as do other tests for antibodies to streptococcal antigens: the fact that not all titers found in acute rheumatic fever fall out of the entire range of titers found in the presumably normal population. However, two aspects of this neutralization test remain to be explored. First, the sensitivity of the anti-hyaluronidase test as compared with tests for antibodies to other streptococcal antigens, in cor-

relation with variations in clinical phase of the disease and, second, the possibility that simultaneous performance of the anti-hyaluronidase test and one of these other tests may yield more striking differences between normal subjects and patients with active rheumatic fever than any one test alone. These questions are now under investigation, the results of which will be reported elsewhere.<sup>3</sup>

**Summary.** The mucin-clot prevention test for the measurement of hyaluronidase *in vitro* has been applied to the measurement of neutralizing antibodies to streptococcal hyaluronidase in serum. The reliability of this test has been confirmed by comparison with spreading potency of the hyaluronidase in the skin, and the specificity of the test for enzyme of streptococcal origin has been confirmed by comparative tests with pneumococcal, clostridial and testicular hyaluronidase.

Streptococcal anti-hyaluronidase has been found in the sera of presumably normal human beings: at mean titers of 46 in neonatal infants, less than 8 in infants, 36 in children, and 30 in young adults.

In a typical acute streptococcal infection, scarlet fever, the mean anti-hyaluronidase titer in 130 individuals was found to be 73 at the third week after the onset of the illness, in comparison with 20 during the first few days. In some children the titer continued to rise after the 3rd week.

In patients with quiescent rheumatic fever the findings were comparable to those in normal children. In 100 patients with acute rheumatic fever, however, the geometric mean titer was 580, 84% of the individual titers being higher than the entire range found among quiescent rheumatics.

The possible implications of these findings are discussed in terms of the epidemiology of streptococcal disease

and the serologic diagnosis of acute rheumatic fever.

NOTE: Since this report has gone to press a paper has appeared in which it was found that the mean titer to

streptococcal hyaluronidase in sera of patients with rheumatic fever was significantly higher than the mean titer in sera obtained from convalescents of streptococcal infections, other infections and normal individuals.<sup>16</sup>

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# ALLERGIC CARDIOVASCULAR DISEASE, WITH REPORT OF TWO CASES OF PERIARTERITIS NODOSA

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THE concept of a single basic pathologic process producing a variety of syndromes has increasingly occupied medical thought since Philippe Ricord<sup>25</sup> corresponded with the Union Medicale on syphilis. Ricord recognized that the reaction of a tissue to a specific agent may vary widely and believed that functional impairment is more dependent on the organ involved and magnitude of the involvement than on the agent producing the damage. The first of these concepts, variability of tissue response to a specific injurious agent, was greatly elucidated by the studies of Opie<sup>20</sup> and of Rich<sup>22</sup> in their investigations of allergic inflammations to determine local tissue injury and reaction.

It has become equally well established that different injurious agents can cause the same type of tissue reaction. Widespread vascular lesions have in recent years been noted as prominent features of such diseases of obscure etiology as periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus, thrombo-angiitis obliterans, and diffuse scleroderma. The fibrinoid degeneration occurring in each has suggested a common basic factor in etiology (Banks<sup>3</sup>, Klemperer, Pollack, and Baehr<sup>17</sup>). Since this alteration of connective tissue appears identical to that seen in serum sickness, in the Arthus phenomenon, in drug

sensitivity, and in experimental protein hypersensitivity, there has been much discussion as to whether the supposed common factor is one of allergy. Baehr and Pollack<sup>2</sup> in a critical analysis point out that since fibrinoid degeneration represents only a diffuse injury of unknown nature, it cannot be used as evidence that the reaction in all cases is one of hypersensitivity. Klemperer<sup>16</sup> likewise has warned against use of the argument that a related pathogenesis is indicated by the morphological similarity of lesions, which was excellently demonstrated in a recent study by Bergstrand.<sup>4</sup>

Periarteritis nodosa is the disease of this group in which the evidences of an allergic antecedent have been best demonstrated. Since first suggested by Gruber<sup>11</sup> in 1923, the appearance of allergic manifestations in many periarteritis nodosa victims and the presence of eosinophils in the lesions have favored the probability of hypersensitivity in its pathogenesis. Although eosinophilia was recorded in only 19% of 101 cases collected by Harris, Lynch, and O'Hare<sup>14</sup>, it is frequently transient and may be missed unless many blood examinations are made. Bronchial asthma was noted in 18% of 300 cases of periarteritis nodosa analyzed by Wilson and Alexander<sup>27</sup>. When other atopic disorders like vasomotor rhinitis and urticaria were included, the



incidence of atopy in this disease was increased to 25%. Additional evidence was provided by the observations of Rich<sup>23,24</sup>, who found lesions of periarteritis nodosa in autopsies of patients who shortly before death had become sensitized to serum, to sulfonamides, and to iodine. Rich and Gregory<sup>25</sup> were able experimentally to produce typical lesions in rabbits by injections of sterile horse serum. However, Alston, Cheng, and Short<sup>1</sup> failed to duplicate these lesions in their rabbits, using a similar procedure.

As emphasized by Harkavy<sup>13</sup>, periarteritis nodosa seems to represent an advanced phase of hyperergic vascular disease. The nature of the sensitizing allergen is of therapeutic importance, because desensitization to the antigen or its removal would appear a possible method to halt the process. Although drugs and sera have been shown capable of producing periarteritis nodosa, in the majority of cases no such factor can be determined. Reimann, Price, and Herbut<sup>21</sup> suggested hypersensitivity to the trichina antigen as the basis of development of lesions in 2 cases occurring in trichinosis. Contratto<sup>7</sup> believed one of his cases to be the result of allergic response to active glandular tuberculosis. Bacteria are considered the most frequent sensitizing agent, and periarteritis nodosa has been observed to follow infections with various bacteria, particularly hemolytic streptococci. In such cases Miller and Daley<sup>12</sup> believe it is rational to employ antibiotics to eliminate the causative agent and perhaps produce a cure.

The disease has been regarded as usually fatal, but this view may well be due to the fact that most cases have been recognized at necropsy and that cases diagnosed during life are usually far advanced. Recovery or

unusually long remission after diagnosis by biopsy has been occasionally reported (Carlin and Hicks<sup>6</sup>, Contratto<sup>7</sup>, Goodman<sup>10</sup>). There has been one apparent cure with sulfapyridine (Goldman, Dickens, and Schenken<sup>22</sup>).

The clinical manifestations of periarteritis nodosa depend upon the tissues embarrassed by the vascular reaction. Since the lesions occur in crops and occasionally involve only 1 or 2 systems, there may be much variation in the symptoms and signs. In 1878 Meyer<sup>18</sup> established the diagnostic triad of chlorotic marasmus, polymyositis and polyneuritis, and gastrointestinal symptoms. Glomerulonephritis was later added by Brinkmann<sup>5</sup>, and cerebral and cutaneous involvement by Harbitz<sup>12</sup>. Familiarity with the usual manifestations as described in extensive analyses and a high index of suspicion have led to more frequent diagnoses during life. Evidences of a widespread system involvement not explainable by a single, more common, disease, or an atypical course of a suspected common condition may lead to consideration of the presence of periarteritis nodosa. If allergic manifestations are also present, the likelihood of the condition is increased. Palpable nodules along the arteries are extremely significant, but occur in a minority of cases. A positive diagnosis during life can be suspected by the clinical course, but can be made with certainty only by the microscopic examination of diseased tissue. A biopsy may be taken of affected muscle or skin, or of palpable nodules along the course of the vessels. Occasionally a diagnosis may be made in unsuspected cases by examination of tissues removed at operation when a surgical condition is simulated.

The morphology of periarteritis nodosa is a disseminated focal panarteritis, which may be spotty in its dis-

tribution. The functional pathology is that of multiple, rapidly developing occlusions of small arteries to produce widespread miliary infarcts. Periarthritis nodosa is a disease of small muscular arteries, and characteristically spares the large elastic arteries and the arterioles. The process involves all coats of the vessels, but begins with a coagulation necrosis of the muscular media. The initial medial degeneration is followed by a thrombosis and neutrophilic leukocytic congregation. There then develops a subacute granulomatous inflammation, sometimes with numerous eosinophilic leukocytes among the lymphocytes, neutrophils, and histiocytes. The last stage in the primary lesion is a chronic productive inflammatory reaction with eventual canalization of some of the vessels. The changes in the surrounding tissues supplied by these vessels are successively albuminous degeneration, coagulation necrosis, and eventual replacement fibrosis. Multiple aneurysms are present in about 10% of the cases.

The following 2 cases, recently studied at our School of Medicine, are reported because they presented definite clinical evidence of hypersensitivity.

**Case Reports.** CASE 1. M.D., a 63 year old white housewife, was admitted to John Sealy Hospital on November 19, 1946, complaining of intermittent darting pains in her hands, feet, and back for 7 weeks. The pains had been accompanied by soreness of her tongue, and since they began, she had lost about 30 pounds in weight. There had been several episodes of fever to 102°F., each lasting several days. Her past history revealed good health until 1940, when she developed occasional episodes of right upper abdominal pain. In 1941 for the first time she began having frequent attacks of wheezing and shortness of breath. The attacks of dyspnea occurred at all times of the year, and for several months had been accompanied by symptoms of hay fever. For several years she had been on a self-imposed diet of toast, butter, and milk. Sensitivity

tests done 6 months prior to admission were positive for coffee, lemon, potato, and feathers. There was no previous personal or familial history of allergy.

Examination revealed a chronically ill middle-aged female who appeared mentally dull. There was brownish pigmentation of the dorsal surfaces of the hands and elbows. The blood pressure was 148/76, pulse 90, temperature 100°F. Conjunctivae and mucous membranes were pale, and the tongue was atrophic with redness at the margins. The fundi showed some increase in tortuosity of the arteries but no nodularity. The heart was moderately enlarged to the left with soft systolic murmurs heard in the aortic and mitral areas. The lungs were clear, and abdomen negative. Arteries showed increased thickness, but no nodes or areas of tenderness. There was a moderate generalized atrophy of the musculature. Mild tenderness in the muscles and along the nerve trunks was noted. There was absence of the right biceps and left patellar reflexes, the remainder of the deep reflexes being hypoaactive. No pathological reflexes were demonstrable. There was marked impairment of all forms of sensation in the extremities.

The red count was 2.47 million with 8.8 gm. of hemoglobin. The white count was 18,700, with 68% neutrophils, 15% eosinophils, 6% lymphocytes, and 11% monocytes. All subsequent counts showed 20 to 35% eosinophils. Urinalysis showed a maximum concentration of 1.018, trace of albumin, 5 to 10 red cells and 1 to 3 white cells per high power field. Occasional hyaline and coarsely granular casts were seen. Red cells were a constant feature of all urinalyses. Blood Kahn and Kolmer were negative. Stool examinations, routine agglutinations and blood cultures were negative. Gastric analysis showed free hydrochloric acid. Non-protein nitrogen on admission was 47 mg., later rising to 78. Serum calcium was 9.2 mg., phosphorus 3.3 mEq., and alkaline phosphatase 3.9 Bodansky units. Serum proteins were 6.8 gm. total, with 4.9 gm albumin and 2.7 gm. globulin. Lumbar puncture showed pressure of 120 mm., with normal spinal fluid. Electrocardiogram revealed a right bundle branch block of the Wilson (S<sub>1</sub>) type. A teleroentgenogram of the chest showed marked enlargement of the transverse diameter of the heart and aortic arch. Lung fields demonstrated diffuse clouding, with mottled shadows and beading along the bronchovascular pattern. A deltoid muscle biopsy was diagnostic of periarthritis nodosa.

The patient ran a downhill course, with increasing stupor and remittent temperature. Urine output was about 500 cc. per day. She became anuric immediately after being given Diodrast intravenously for pyelography on her 10th hospital day. A skin test prior to the injection had been negative. During the next 3 days she passed a total of only 18 cc. of urine. She expired in uremia on her 13th day of hospitalization, during an attempted decapsulation of the right kidney.

**POSTMORTEM EXAMINATION:** The pertinent gross necropsy findings were: 1. Multiple small hemorrhages over the anterior abdominal wall and flexor surfaces of the extremities. 2. Dilated and hypertrophied heart (430 gm.), with yellowish nodular lesions along

**CASE 2.** A.M., a 38 year old colored farmer, entered John Sealy Hospital on August 17, 1946, because of marked respiratory distress. His illness began 5 weeks prior to admission, with dyspnea on exertion. This was followed 2 weeks later by intermittent episodes of precordial pain, each lasting from several minutes to 2 hours. A progressive dependent edema then began, and 5 days before admission there developed a massive anasarca. Since the age of 28 there had been rare episodes of mild joint pains involving the ankles and knees, not accompanied by redness or swelling. In June, 1946, there had been noted an acute dermatitis involving the nose and malar regions, which disappeared in a few days to leave areas of increased pigmentation.

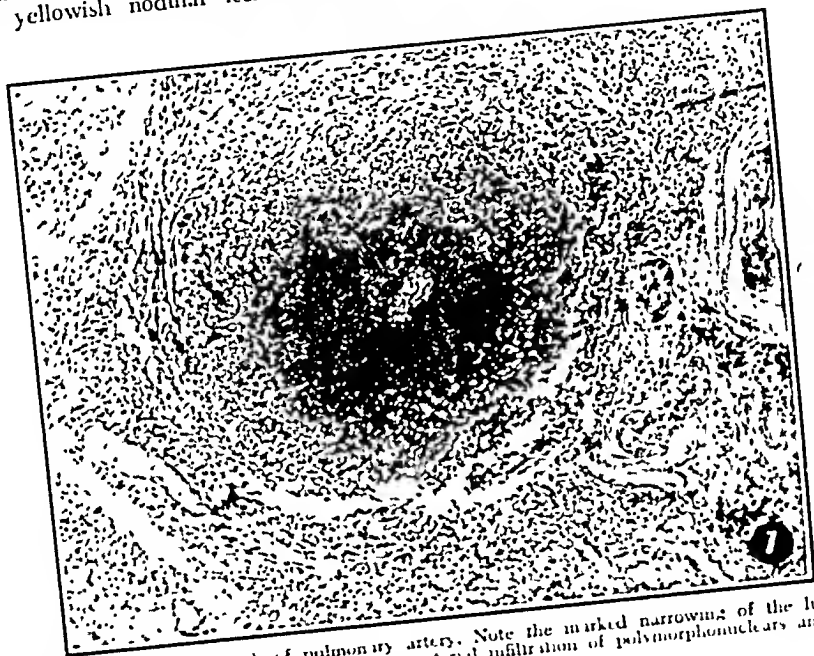


FIG. 1. Case 1. Small branch of pulmonary artery. Note the marked narrowing of the lumen, inflammatory reaction in all coats of the vessel, and perivascular infiltration of polymorphonuclears and eosinophils.

the smaller arteries of the epicardium. 3. Scattered yellow milium cysts of the hepatic portal tracts and gall bladder serosa. 4. Swollen pale kidneys (270 gm.). 5. 260 gm. heart, with many sub- and intraparenchymal dark-red and yellow milium cysts. 6. Minute yellow nodular lesions along the small arteries throughout the cortex, white nodules of varying sizes of the small yellowish organs all were in varying degrees

On examination this hyposthenic colored male was markedly dyspneic, with marked edema involving the extremities, genitalia, and trunk. The blood pressure was 170/90, and pulse 120. A paraxillary pulse was present. Both malar eminences and bridge of the nose showed irregular brownish discoloration without atrophy. There was marked distention of the neck veins, and moist rales were heard over both lung fields posteriorly. The heart was markedly enlarged, and sounds were distant. A pericardial friction rub was heard soon after admission. Neurological examination was negative.

The red count was 3.2 million with hemoglobin 64%. The white cell count was 16,400, and differential showed 91% segmenters, 4% stabs, and 5% lymphocytes. Urinalysis revealed maximum specific gravity of 1.017 and four-plus albumin. There were 50 red cells and 30 white cells per high power field. Non-protein nitrogen was 72 mg. per 100 cc; blood cholesterol, 186 mg. The sedimentation rate (Wintrobe) was 25 mm./hr. The blood Kahn was positive, and Kolmer anti-complementary. Fluoroscopy showed the presence of a pericardial effusion, and 250 cc. of blood-tinged fluid was withdrawn from the pericardium. The specific gravity of the fluid was 1.020, cultures being negative. It con-

of dyspnea and anasarca after he discontinued his digitalis. Blood pressure was 188/108, and there was marked generalized edema. Cardiac enlargement was marked, and there were frequent moist rales at the lung bases. The red count had fallen to 1.95 million with hemoglobin 29%. The white cells numbered 8,700 per c.mm., and the differential count showed 6% eosinophils. Urinalyses were the same as previously. Non-protein nitrogen was 62 mg. The plasma proteins were 6.2 gm., with albumin 2.6 gm., and globulin 3.6 gm. Electrocardiogram showed little change. Despite redigitalization, the patient gradually became worse. On November 13 there developed many urticarial wheals over the skin



FIG. 2. Case 1. Longitudinal section of a small artery in the kidney. The changes in the vessel wall have caused a localized weakness to form a small aneurysm. There is a thrombus in the aneurysm with scattered inflammatory cells.

FIG. 3. Case 2. Small branch of coronary artery. The process is of longer duration, and fibroblastic proliferation has replaced some of the acute inflammatory reaction seen in Fig. 1.

tained 6,850 white cells per c.mm., with a differential count of 94% polymorphonuclears and 6% lymphocytes. Electrocardiogram presented low complexes throughout, and negative T in Leads I, II, and IVF. A muscle biopsy was taken from the deltoid, and showed moderate endothelial hyperplasia of small arteries and some increase in sarcolemma nuclei. Following digitalization, low sodium diet, and diuretics, there was much improvement, and patient was discharged on October 1.

2nd Admission (18 days later): The patient was readmitted because of recurrence

of the trunk with intense itching, and these persisted 5 days. The patient subsequently developed increasing cardiac failure and expired on the 42d day of hospitalization.

**POSTMORTEM EXAMINATION:** The pertinent gross findings at necropsy were: 1. Macular pigmentation of both malar eminences. 2. Moderate edema of external genitalia and lower extremities, with 1000 cc. of clear, yellow fluid in the abdominal cavity. 3. Obliteration of pleural and pericardial cavities by thick, fibrous adhesions. 4. Heart and pericardium weighing 650 gm., with petechial hemorrhages throughout the epicar-

dium. 5. Kidneys (210 gm. each) showing numerous milium red and yellow areas in the cortex and medulla. Microscopic examination demonstrated a conspicuous nodular periarteritis of the small arteries of the heart (Fig. 3). The myocardial stroma was edematous, and in the region of the diseased vessels was infiltrated with groups of polymorphonuclears and eosinophils. In some areas proliferating fibroblasts could be seen. The lungs showed moderate venous congestion, and the septa were thickened and infiltrated in several areas with eosinophilic leukocytes. Some of the small arteries in the lungs showed inflammation of all their coats and thrombosis. Kidneys showed hyalinization of many glomeruli, foci of chronic inflammatory cells, and replacement fibrosis.

**Discussion.** The first patient presents most of the clinical manifestations typically seen in periarteritis nodosa. Allergic phenomena were prominent, as evidenced by the episodes of bronchial asthma and hayfever, and a constant eosinophilia of 15 to 35%. The fever, anemia, weight loss, and weakness were conspicuous but non-specific signs. Widespread system involvement was indicated by the polyneuritis, myositis, nephritis, abnormal cardiac findings, and mental changes. The radiological manifestations in the lungs such as seen in this patient are similar to those seen in Loeffler's syndrome, and were previously described by Herrmann.<sup>15</sup> On histological examination the pulmonary infiltrations were found to be composed of periarthritic accumulations of eosinophils. The characteristic pathologic picture was demonstrated in the biopsy specimen.

Although the skin test for Diodrast was negative and there was no history of iodine sensitivity, the intravenous injection of Diodrast evidently precipitated an anuria in the previously diseased kidneys. The patient was oliguric before its administration, but voided at least 500 cc. of urine with a maximum specific gravity

of 1.018. Immediately after the unsuccessful attempt at pyelography, there was a sudden cessation of urine output. The total quantity of urine excreted in the 3 remaining days of life was only 18 cc. Furman<sup>8</sup> in a recent review of the American literature found 36 cases of fatality from the administration of 35% Diodrast, 2 of which were due to acute renal shutdown presumably caused by this drug. He emphasized the unreliability of the intracutaneous test and regarded the oral and ocular tests as more dependable. It would seem from our experience that Diodrast should be administered with caution to patients with suspected periarteritis nodosa, especially if there are indications of poor renal function or hypersensitivity. As sensitivity to iodine has been reported as actually producing periarteritis nodosa,<sup>21</sup> in such a situation Diodrast administration would be particularly dangerous.

The second patient represents a diagnostic problem which was solved only at necropsy. The heart and kidney were the organs predominantly involved by the pathological process, and there were clinical signs of nephritis, pericardial effusion, and cardiac failure. Arthritic symptoms such as presented by this patient are reported in 27% of the cases analyzed by Harris, Lynch, and O'Hare.<sup>14</sup> Allergic manifestations were transient and easily overlooked, consisting of a 6% eosinophilia on a single examination and one episode of urticaria. The endothelial hyperplasia of the small arteries in the biopsy specimen may have represented an early change of the disease, but it was not thought to be significant.

The role of the dermatitis in the disease process is difficult to evaluate because it had disappeared by the time

the patient was seen. The only residuum was a spotty hyperpigmentation of the malar eminences and bridge of the nose, and there was no evidence of scaling or atrophy. Although lupus erythematosus was considered, it was concluded from the description given that the diagnosis was most probably erysipelas. Since the symptoms began soon after the episode of dermatitis, sensitivity to the hemolytic streptococcus causing the cellulitis may well have been the etiology of the vascular reaction. It is doubted that administration of antibiotics would have been of benefit, for the dermatitis had already subsided spontaneously.

**Summary:** 1. The evidences for a basic factor of allergy in diffuse vascular disease of obscure origin are discussed, with particular reference to periarteritis nodosa.

2. Clinical characteristics and the pathology of periarteritis nodosa are summarized.

3. Two cases of periarteritis nodosa are reported, one of which was diagnosed during life. Sensitivity to Diodrast is regarded as the cause of acute anuria and death in the first case. In the second patient the lesions may well have developed as an allergic response to the hemolytic streptococcus. Both cases show allergic features, although in the latter they were transient.

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# INCIDENCE OF THE BLOOD GROUPS AND THE SECRETOR FACTOR IN PATIENTS WITH PERNICIOUS ANEMIA AND STOMACH CARCINOMA\*

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IN a previous discussion of gastric cancer<sup>1</sup> it was suggested by one of us (A.C.I.) that there might be a relationship between the occurrence of gastric carcinoma and the blood groups and/or Rh negativeness. Bases for this assumption were several. The agglutinogens A and B are concentrated in the gastric mucus; heredity is concerned in the determination of blood groups; it is possible that premature achlorhydria, pernicious anemia and the predisposition to cancer of the stomach are hereditary; and patients with pernicious anemia seem to be predisposed to gastric cancer. This survey of the incidence of the blood groups (O, A, A<sub>1</sub>, A<sub>2</sub>, B, AB, A<sub>1</sub>B, A<sub>2</sub>B, M, N, MN, Rh<sub>0</sub> positive and Rh<sub>0</sub> negative) as well as the secretor or non-secretor attributes, was undertaken in the attempt to determine whether any relationship existed between them and pernicious anemia and stomach carcinoma. We have further attempted to determine whether there was any relationship between the ability to secrete group specific substances in the saliva and the occurrence of pernicious anemia. The ability to secrete group specific substances in the saliva has also been correlated with the gastroscopic findings in a number of these patients with the possibility in mind that the ability to secrete these substances in the saliva

might be related to the character of the gastric mucosa. The gastroscopic findings in our patients have previously been reported<sup>2</sup>. The blood types and secretor or non-secretor ability have also been investigated in a small group of cases of carcinoma of the stomach as part of this study.

Blood group specific substances are present in the cells of almost all organs and tissues of the body, and are also present in the body fluids of secretor individuals<sup>3</sup>. In man these substances occur in the blood and other body cells in combination with lipids to form alcohol-soluble compounds. In the body fluids of secretors the group specific substances are present in an uncombined water soluble form, absent in non-secretors.<sup>3a</sup> Bray and his co-workers<sup>1</sup> isolated a mucopolysaccharide from gastric mucin which gave serological reactions similar to group specific substance A. The possibility that such a mucopolysaccharide may have a protective action against the development of carcinoma of the stomach is speculative at present. Approximately 82% of all Caucasians secrete blood group specific substances in their body fluids, while 18% fail to do so.<sup>3b</sup> Saliva and gastric juice contain the highest concentration of these substances in secretor individuals.<sup>3c</sup> The ability to secrete blood group specific

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substances (the "secretor" character) is transmitted as a simple Mendelian dominant and no evidence has been found of the linkage of this character with the inheritance of any of the agglutinogens.<sup>8d</sup> The trait is constant, and when group specific substances are lacking in the saliva they are also lacking in all other body fluids.<sup>8e</sup>

In a related study by Witebsky, Klendshoj and Vaughan<sup>10</sup> it was concluded that the gastric juice of persons with pernicious anemia contained group specific substances in at least the same amounts as normal gastric juice, in spite of the fact that there was no free hydrochloric acid or pepsin in the specimens. They determined the occurrence of blood group specific substances in the gastric juice and saliva of 12 persons with pernicious anemia and found that 11 of the 12 were secretors and one was a non-secretor. Seven of their cases had group O, 4 group A, and 1 group AB blood.

The relationship between pernicious anemia, the concomitant atrophy of the gastric mucosa, and the predilection for the development of gastric carcinoma has been discussed by numerous authors.<sup>5 a,b,c,d</sup>

**Material.** One hundred and sixty patients with pernicious anemia, who were in regular attendance at the Anemia Clinic of the Cook County Hospital (Chicago) were used in this study. Of these, 119 were white and 41 negro. The diagnosis of pernicious anemia had been established and substantiated by the usual criteria. Five of the patients with pernicious anemia had also been found to have carcinoma of the stomach by X-ray examination, gastroscopy, and/or surgical exploration and tissue examination. These cases are included in the pernicious anemia series and are also considered with the 10 cases of carcinoma of the stomach, similarly diagnosed, but not having pernicious anemia.

We have assumed, as did Schiff,<sup>6</sup> that the incidence of secretors and non-secre-

tors in group O individuals was the same as in the remainder of the population. This assumption was made because of the difficulty in preparing or obtaining an anti-O serum and for this reason, no attempt was made to test the saliva of group O individuals for the secretor trait.

**Methods:** Five cubic centimeters of venous blood were collected from each patient. The blood was allowed to clot in the refrigerator and later a 2% cell suspension in saline was prepared and used at once. Blood grouping was done by the standard slide method, employing 1 drop of freshly prepared 2% cell suspension in saline against an equal sized drop of Anti A and Anti B serum. Each cell suspension was separately examined to exclude autoagglutination. Readings were made at 5 minutes macroscopically and checked by means of a hand lens. All serums used for blood grouping met the requirements of the National Institute of Health.

M and N typing was also performed by the slide method.

Subgrouping individuals of groups A and AB was done on the slide by mixing 1 drop of a 2% freshly prepared cell suspension and 1 drop of absorbed B serum. Readings were made microscopically after 10 minutes of gentle agitation. The presence of agglutination indicated that the cells were of subgroup A<sub>1</sub>, A<sub>1</sub>B.

Rh typing was performed by the standard Rh slide method using only Anti Rh<sub>0</sub> (Anti D) serum.

Saliva was obtained from all patients. It was collected in test tubes, placed in a boiling water bath for 20 minutes, in order to inhibit destructive enzymes, and then refrigerated. All saliva specimens, except those from group O persons, were tested within 5 days by the inhibition of agglutination method described by Wiener.<sup>3f</sup> The saliva was diluted 1:10 before using and the specimen was read microscopically for agglutination after gentle agitation of the tube to dislodge the clump at the bottom. Strongly positive subgroup A<sub>1</sub> and group B cells were selected and used in 2% solution in saline. Serums used\* for the saliva typing were prepared by preliminary saline dilution of stand-

\* Prepared by a laboratory licensed by the National Institute of Health.



ard blood grouping serums, the diluted material showing a specific titre of 8 (Wiener technique) to 16 (National Institute of Health technique). The results of these tests are given in Table 1.

**Findings.** 1. There were fewer group O individuals who had pernicious anemia than would have been expected on the basis of group O incidence in the general population. This deviation from the normal is statistically significant and is not explained. It is not due solely to the stated predilection of the disease for Scandinavians,

anemia, the percentages of individuals in subgroups  $A_1$  and  $A_2$  correlate statistically with the normal group, but the ratio  $A_2/A_1$  is deviated in a statistically significant amount from the normal. Absorbed B serums differ greatly in titre and this could account for the variations from the normal in the subgrouping of A which we have obtained.

3. Other than the above mentioned deviations, the 160 persons with pernicious anemia fell into groups comparable with large unselected series of

TABLE 1. INCIDENCE OF BLOOD GROUPS AND SALIVARY SECRETOR FACTOR IN 160 PATIENTS WITH PERNICIOUS ANEMIA (5 ALSO WITH CARCINOMA OF STOMACH) AND 10 PATIENTS WITH ONLY CARCINOMA OF STOMACH

	WHITE			NEGRO			TOTAL		CARCINOMA OF STOMACH		
	Num-ber	%	Normal %	Num-ber	%	Normal %	Num-ber	%	with P.A.	with- out P.A.	Total
Male	61	51		14	34		75	47	4	9	13
Female	58	49		27	66		85	53	1	1	2
O	34	28	45.0 (8g)	20	48	44.2 (8h)	54	34		8	8
A	62	52	41 (8k)	16	39	30.3 (8l)	78	48	4	2	6
$A_1$	52	43	29 (8m)	12	29	19.6 (8n)	64	40	4	1	5
	0.19	$\frac{A_2}{A_1} =$	$\frac{A_2}{A_1} =$ (8m)0.16	0.33	$\frac{A_2}{A_1} =$	$\frac{A_2}{A_1} =$ (8n)0.67					
$A_2$	10	8.3	8.9	4	9.8	6.8	14	8		1	1
B	17	14	10.0	4	9.8	21.8	21	15	1		1
AB	6	5	4.0	1	2.4	3.7	7	4.3		1	1
$A_1B$	4	3.3	5.2			1.6	4	2.5			
$A_2B$	2	1.6	1.4	1	2.4	1.1	3	2		1	1
			(8i)			(8j)					
M	40	33	20.16	12	29	28.42	52	33	2	6	8
N	24	20	21.26	9	22	21.94	33	20		2	2
MN	55	46	40.58	20	48	49.64	75	47	3	3	6
			(2)			(7)					
Rh <sub>0</sub> +	107	91%	85.8	39	95	91.2	146	91	4	8	12
Rh <sub>0</sub> neg.	12	9	14.2	2	4.8	9.8	14	9	1	3	4
			(8o)			(8p)					
Secretor	66	78	82.0	12	57	61.2	78	73	4	3	7
Non Secretor	19	22	18	9	43	38.8	28	27	1		1

The figures in parentheses, like the superscript numbers in the text, indicate the source in the list of references.

Irish, and English<sup>9</sup> for, while the Scandinavians have fewer type O individuals than the United States normal, the Irish and English show a greater percentage.<sup>8q</sup>

2. The percentage of white pernicious anemia patients in subgroup  $A_1$  is greater than in the general population and this deviation is also statistically significant. However, the  $A_2/A_1$  ratio correlates with the normal. In the negro patients with pernicious

the United States white and negro population as regards their major, minor, and blood sub-groups, as well as their secretor and non-secretor ability.

4. The number of patients in this series with carcinoma of the stomach is small (15 patients) but seems to show a normal trend in blood groups and the distribution of the secretor trait.

5. Comparison of secretor and non-secretor individuals with regard to their gastroscopic findings revealed ap-

proximately the same percentage of gastric atrophy (either localized or generalized) in both groups (Table 2).

**Conclusions.** 1. The occurrence of pernicious anemia is not definitely related to the blood groups or Rh negativity.

2. Patients with pernicious anemia secrete blood group specific substances in their saliva in the same proportion

as normal individuals.

3. The percentage of secretors and non-secretors was approximately the same in pernicious anemia patients who showed gastric atrophy as it was in those who had a normal gastric mucosa.

4. Patients with carcinoma of the stomach show an approximately normal distribution of blood groups and of the secretor trait.

TABLE 2. COMPARISON OF GASTROSCOPIC FINDINGS IN SECRETOR AND NON-SECRETOR INDIVIDUALS

	Negative	Localized Gastritis	Generalized or Extensive Gastritis	Carcinoma	Polyps	Benign Ulcer	Not Gastroscooped	Gastroscooped	% showing local or generalized atrophy
Secretors (78 cases)	20	19	4	1	3	1	30	48	48%
Non-Secretors (28 cases)	8	10	2	1	0	0	7	21	57%

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# THE ROLE OF PLATELETS IN THE COAGULATION OF THE BLOOD\*

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WITH the development of means to determine prothrombin quantitatively and with the coincidental discovery of vitamin K, interest in coagulation has in recent years been centered mainly on prothrombin. Knowledge concerning the other factors such as thromboplastin, calcium and platelets has not advanced proportionally and a number of investigators either ignore these factors or complacently use, as in the case of thromboplastin, almost any type of preparation with little consideration as to its purity or potency.

The issue concerning the platelets is clear cut: either they play no direct role in coagulation, or they are the very key upon which the whole hemostatic mechanism revolves. It is the purpose of this paper to offer observations that will help to settle this basic problem.

An extensive historical discussion is dispensable since adequate reviews are available.<sup>13,17,19</sup> It should be mentioned, however, that both Bizzozero<sup>1</sup> and Hayem<sup>6</sup> came to the conclusion from microscopic studies that a substance is liberated from disintegrating platelets that directly participates in coagulation. Their type of study has

been extended by Fonio and Schwendener<sup>1</sup> who agree entirely with this historic view. Morawitz<sup>14</sup> postulated that the platelets supplied thromboplastin, and this plausible explanation of their action gained wide acceptance. Hayem<sup>7</sup> made the important observation that a decrease in platelets did not affect the speed of coagulation but caused an absence of clot retraction. LeSourd and Pagniez,<sup>11</sup> and Bordet and Delange<sup>2</sup> supplied an additional important observation: namely that only intact platelets could effect clot retraction. While the majority of investigators have tacitly accepted that platelets supply thromboplastin, a few workers deny that platelets play an indispensable role in coagulation. Nolf has always maintained that all the essential agents of coagulation are present in the plasma. Lenggenhager<sup>10</sup> summarily dismisses the platelets as having any part in the coagulation reaction. He postulates that a substance he calls prothrombokinin is changed by contact with a foreign surface to an active form which combines with calcium and prothrombin to yield thrombin. Lozner and Taylor<sup>12</sup> present a similar concept except that they

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call their inactive precursor globulin substance. They state specifically: "that the effects of foreign surfaces on blood coagulation are essentially independent of the intact platelet."

When Jaques and his associates<sup>9</sup> introduced a new agent, a silicone, which presents a surface to which platelets do not adhere, a new approach to the study of platelets was made possible. Jaques and his coworkers were able to show that if the platelets were markedly reduced by centrifugation the coagulation time of the plasma was correspondingly increased. This was confirmed by Brinkhous<sup>3</sup> and Quick.<sup>16</sup> The latter, furthermore, showed that the prothombin consumption was almost reduced to zero in platelet-depleted plasma.

In this study the function of the platelet is studied quantitatively by varying the number of platelets without changing the environmental conditions. The effect on coagulation time, speed of clot retraction, size of clot, and consumption of prothrombin are correlated.

**Experimental.** Blood was obtained from young normal adults by venipuncture. The syringe and needle were coated with silicone. Great care was taken to avoid contamination with tissue juice since this contains active thromboplastin. About 50 cc. of blood were collected and transferred to silicone-coated centrifuge tubes immersed in an ice bath. The syringes were kept in ice prior to use. One-half of the blood was centrifuged for 15 minutes at 4000 r.p.m. in an angle centrifuge. The plasma was transferred by means of a silicone-coated pipette to another tube and again centrifuged for 10 minutes at high speed. The other half of the blood was centrifuged at 800 r.p.m. for 10 minutes. The platelet-rich plasma was immediately transferred to a silicone-coated test tube im-

mersed in ice water. A platelet count was made of the high and the low centrifuged plasma by direct count using 3.8% sodium citrate as diluent. Generally fewer than 20,000 platelets per c. mm. remained in the first, but in the second plasma the count was consistently much higher than in whole blood.

The high and low centrifuged plasmas were mixed in varying proportions to a volume of 2 cc. Immediately after mixing, the test tubes were placed in a water bath at 37°C. The beginning of coagulation and of clot retraction were carefully timed. It is not possible to determine accurately the completion of coagulation, but it can be roughly estimated by the density of the clot. There is a close correlation between the number of platelets and the speed at which the clot becomes opaque. Prothombin consumption was determined by the method of Quick.<sup>15</sup> The prothombin time of serum obtained from hemophilic, or platelet-depleted plasma is 10 to 11 seconds instead of 12 seconds obtained with normal plasma. Due to this peculiar shortening, the estimation of prothrombin in serum as per cent of normal is less accurate than in plasma. Studies made on the blood of 3 cases of thrombocytopenic purpura are included to show the possible significance of the present scheme of investigation to the problem of functional pathology of purpura.

**Discussion.** The results obtained in this study clearly explain why the platelets have frequently been underestimated. If one were to judge the action of the platelets in the coagulation mechanism solely on the coagulation time, completely misleading conclusions would be drawn. It will be observed that the beginning of coagulation occurs nearly as early in the plasma with few platelets as in one

with a large number. Furthermore, since coagulation begins at the top of plasma, the end point for the coagulation time is reached exceptionally early because sufficient fibrin is formed to prevent the flow of blood long before actual coagulation comes to completion. Thus, not only is the coagulation time technically unreliable and even misleading, but it is also physiologically faulty for it measures the behavior of blood under totally artificial surroundings and not how it functions in the lumen of a blood vessel after injury.

mination is theoretically and, as will be pointed out later, practically a far more reliable measure of the true speed of coagulation than is the coagulation time as carried out by the Lee-White or the numerous related procedures.

Direct observation of the progress of the clot is a fairly good guide for estimating coagulation, but it has the disadvantage that it cannot be done on whole blood and even in plasma the end point, which is uniform opacity, does not necessarily mark the completion of coagulation. Clot retraction correlates well with prothrombin con-

TABLE 1. THE CORRELATION OF THE NUMBER OF THE PLATELETS, COAGULATION TIME OF PLASMA, SPEED OF CLOT RETRACTION, SIZE OF THE CLOT AND PROTHROMBIN CONSUMPTION

Tube	1	2	3	4	5	6
Number of Platelets in 1 c.mm. of plasma	20,000	41,000	72,000	96,000	128,000	210,000
Beginning of Coagulation (minutes)	3½	3½	3½	3½	3½	3
Completion of Coagulation (minutes)*	18	16½	16½	15½	13½	10
Beginning of Clot Retraction (minutes)	34	22	20	18	13½	10½
Serum expressed in 1 hr. (cc)	0.45	1.30	1.50	1.70	1.75	1.85
Prothrombin consumed** per cent						
in 1 hr.	0(10)	0(10)	0(11)	20(12)	40(14)	75(19½)
in 2 hrs.	0(11)	20(12)	30(13)	45(13½)	50(15)	78(23)
in 3 hrs.	20(12)	25(12½)	40(14)	45(14½)	55(16)	80(25)
in 24 hrs.	35(13½)	50(15)	65(18)	70(19)	75(21)	87(36)

\* Total uniform opacity of plasma.

\*\* The figures in parenthesis represent the prothrombin times of serum given in seconds. The prothrombin consumption is calculated from these figures.

Far more accurate as a quantitative test of platelet function is the consumption of prothrombin and the speed and extent of clot retraction. The greater the number of platelets the more rapid the prothrombin consumption, i.e. the faster the conversion of prothrombin to thrombin. Below a certain number of platelets, no consumption of prothrombin can be demonstrated. To be sure coagulation occurs, since even with extreme care some platelets disintegrate; consequently some thrombin forms, and it, being an enzyme, will in spite of its minute concentration convert a considerable quantity of fibrinogen to fibrin within the confines of a test tube. The prothrombin consumption deter-

sumption and with the number of platelets, as is clearly shown in Fig. 1 and Table 1. The faster clot retraction appears, the more complete is the final retraction. The process follows in the main the same pattern as coagulation; namely, a relatively long latent period followed by accelerated retraction and finally a slow tapering off.

There still exists considerable confusion concerning the meaning of clot retraction and the basic mechanism involved. Quick<sup>17</sup> has pointed out that a certain degree of adhesion exists between fibrin and the walls of the container. Therefore the inner force, the retraction strength, must be greater than the adhesion power if retraction is to occur. This is the case when nor-

mal blood clots in a glass test tube. Collodion on the contrary has such a great affinity for fibrin, that the retraction force is too weak to counteract this adhesion; consequently no retraction occurs when normal blood clots in a collodion-coated tube, as Hirschboeck<sup>8</sup> first observed.

The bulk of cells is another purely mechanical factor which influences clot retraction. Retraction is most com-

plete in cell-free, but platelet-rich plasma. In polycythemic blood, retraction is poor even though the platelets may be above normal, simply because the relatively weak retractive force cannot cope with the large cell mass and reduce its bulk. Naturally, anemic blood shows relatively good retraction.

Clot retraction is generally held to be the same as the syneresis observed

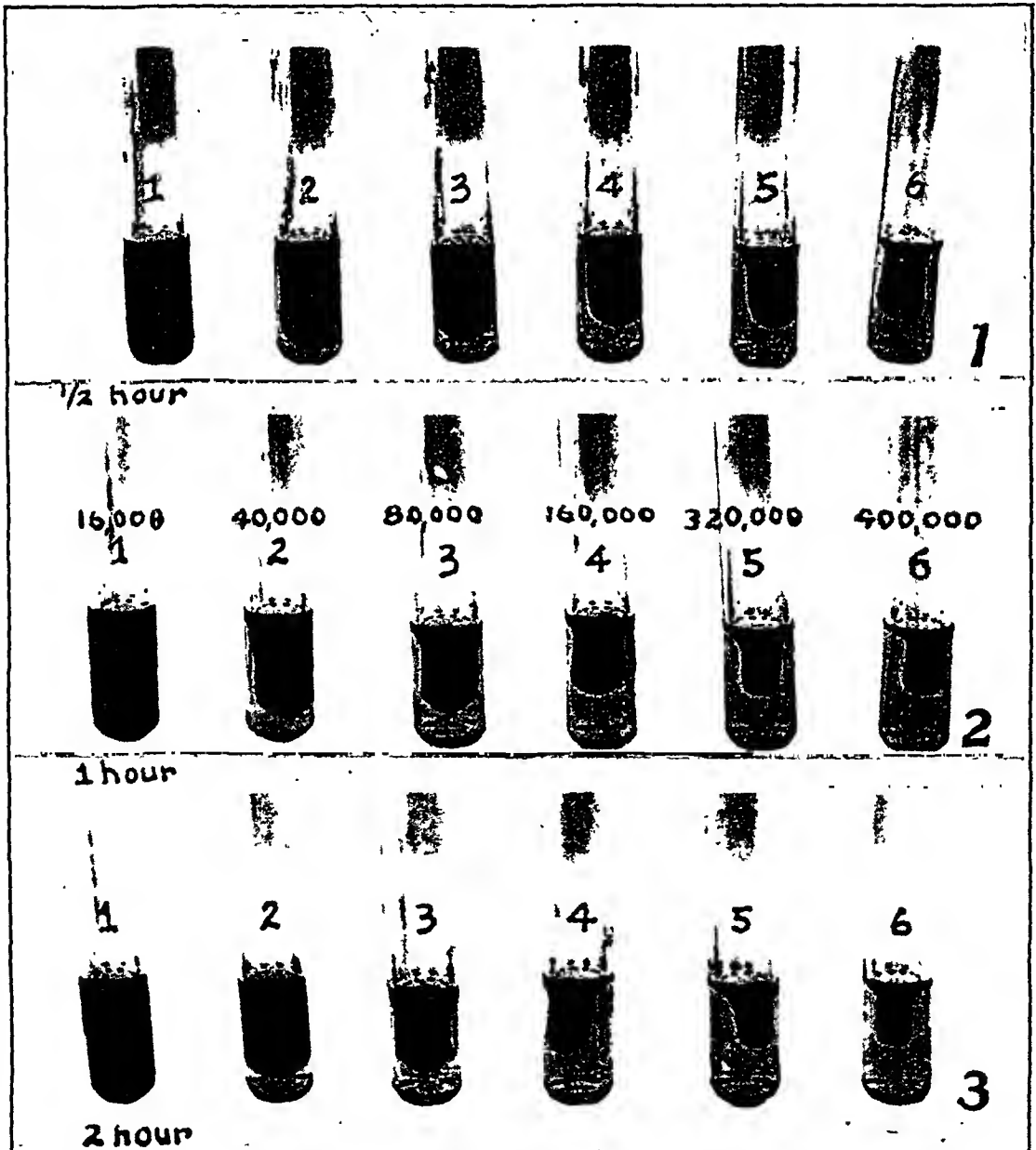


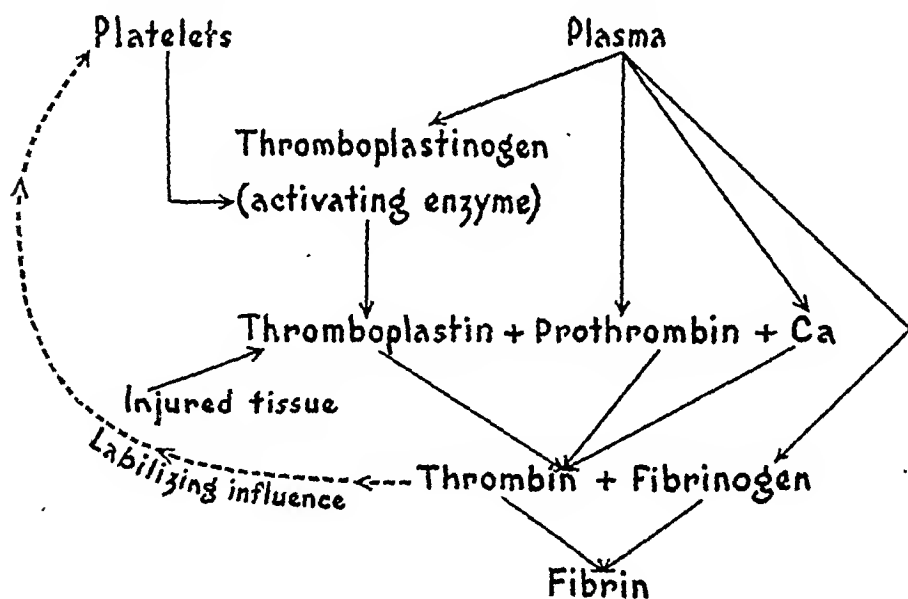
Figure 1.—The Influence of the Number of Platelets on the Speed and Extent of Clot Retraction.

The numbers on the tubes represent platelets per c. mm.

in a colloid gel, but this is probably erroneous, since it is not the completely formed fibrin gel which shrinks but rather the retraction actually occurs during the formation of fibrin. A rational explanation of the process is as follows: due to the formation of a small amount of thrombin resulting either from the rupture of a few platelets or the entrance of a trace of tissue thromboplastin into the blood, a strand or two of fibrin are formed. This immediately serves as a foreign surface on which platelets will adhere and then disintegrate. At this locus of lysis a high concentration of thrombin will form a resulting dense mass of fibrin. The new fibrin supplies again a foreign surface and the high concentration of thrombin acts as a labilizing agent on platelets with the result that the process keeps repeating itself, massing the

fibrin about a small focal point, probably by twisting as Tocantins<sup>18</sup> suggests. When the platelets are diminished, no local areas of high concentration of thrombin occur and therefore the fibrin is evenly distributed throughout the plasma. Since the fibrin strand has no intrinsic power to contract, no shrinking of the clot can occur.

The present findings substantiate further the senior author's<sup>15</sup> hypothesis that the platelets on disintegration liberate an enzyme which is essential for the conversion of thromboplastinogen to active thromboplastin. The reaction between thromboplastin and prothrombin has been shown to be stoichiometric, therefore the amount of thromboplastin made available is directly measured by the prothrombin consumption test. The hypothesis previously offered



#### Stages in coagulation

1. Thromboplastinogen + platelet enzyme → thromboplastin
2. Prothrombin + thromboplastin + Ca = thrombin
3. Fibrinogen thrombin → fibrin

Figure 2.—A Correlation of the Factors Participating in the Coagulation Reaction.

and discussed is presented in diagram form (Fig. 2). It should again be emphasized that physiologically the first or precipitating step in coagulation may be the entrance of a minute amount of tissue thromboplastin into the blood causing the formation of a small amount of thrombin, which not only causes the formation of fibrin to which platelets adhere, but also has a labilizing action on these cells. These

reasonable to conclude that the speed of prothrombin conversion determines hemostatic effectiveness, it is obvious why a diminution of platelets becomes a significant factor in producing a hemorrhagic tendency. It is also to be noted that the platelet enzyme can easily become inactivated. In fact the activation of thromboplastinogen is even incomplete in the coagulation of normal blood, and when the number of

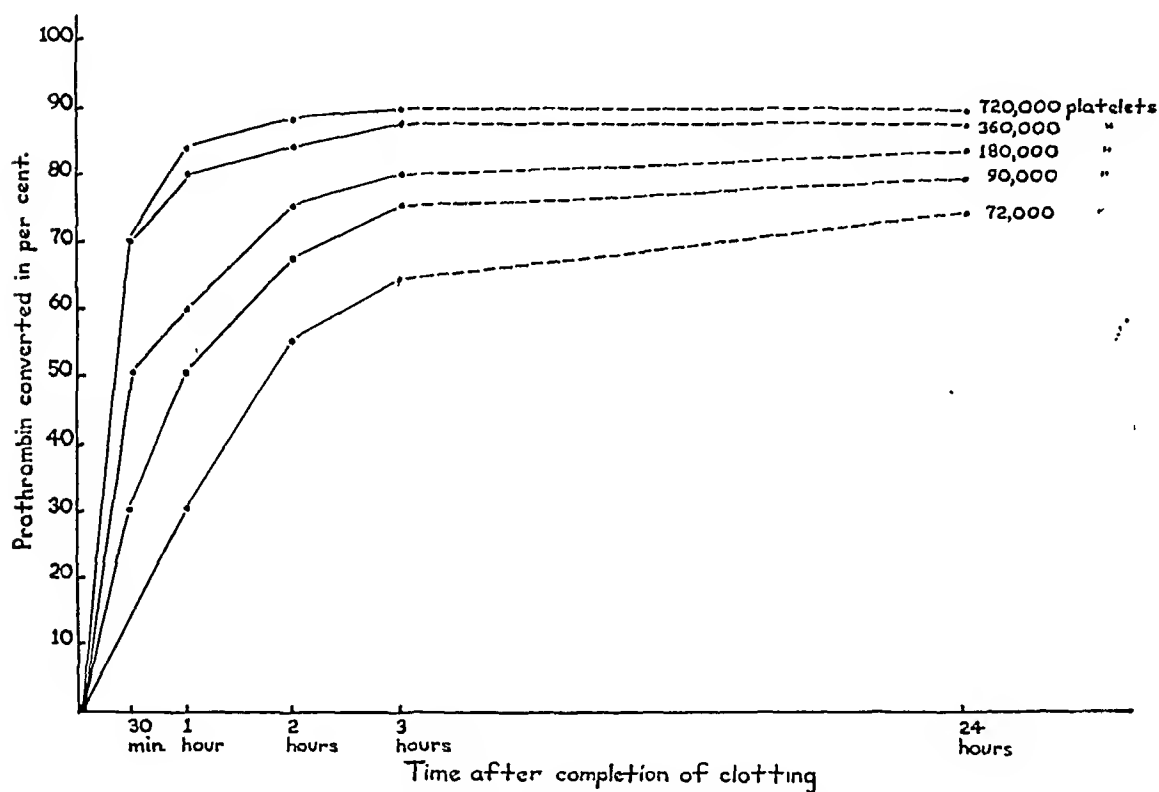


Figure 3.—The Influence of the Number of Platelets on the Speed of Prothrombin Conversion.

2 actions of thrombin cause platelets to begin disintegrating which in turn brings about the formation of more thrombin and thus sets off an autocatalytic or chain reaction.

If one constructs a graph plotting amount of prothrombin consumed against time for plasma containing varying number of platelets, a series of curves are obtained which all tend to approach a fixed final value but the speed is dependent upon the total number of platelets (Fig. 3). Since it is

platelets is reduced, the amount of thromboplastin made available as measured by the prothrombin consumption test may be very small.

An explanation can now be given for the paradoxical observation that the coagulation time is generally normal in thrombocytopenic purpura. A minute amount of platelet enzyme can produce enough thrombin to coagulate sufficient fibrinogen in 5 minutes to form a clot rigid enough to give the coagulation time end-point. The clotting time



therefore is apparently normal, but this does not signify that coagulation is normal, for on determining the prothrombin consumption it is found that only a trace of prothrombin was converted during the first hour after coagulation. In Table 2 the findings of 3 cases of thrombocytopenic purpura are presented. In the 2 cases with distinct low platelet counts the coagulation was normal but the prothrombin consumption was abnormally diminished. These findings can be regarded as showing unequivocally for the first time a definite coagulation defect masked by a normal coagulation time. It will be recalled that the same occurs in hypoprothrombinemia. The normal coagulation time fails to give evidence

lets. Glanzmann also postulated that platelets contain an enzyme, retractozyme, which is specifically responsible for clot retraction. This concept has never been confirmed, and it fails to explain why only intact platelets can cause clot retraction. The explanation of clot retraction offered in this paper makes it unnecessary to postulate any other factor than the enzyme which activates thromboplastinogen.

**Summary.** A technique was devised for varying the number of platelets without otherwise altering the plasma.

The effect of the number of platelets was studied and the following observations made: (1) The greater the number of platelets the sooner clot retraction begins, and the smaller the

TABLE 2. A CORRELATION OF NUMBER OF PLATELETS TO PROTHROMBIN CONSUMPTION IN THROMBOCYTOPENIC PURPURA

Case	Number of Platelets in 1 c.mm.	<u>Prothrombin Consumption in per cent of normal</u>	
		1 hr.	2 hrs.
1	80,000	trace (10 sec.)	trace (10 sec.)
2	29,000	trace (10 sec.)	40 (14 sec.)
3	115,000	50 (15 sec.)	60 (17 sec.)

No clot retraction was observed in Cases 1 and 2. The coagulation time was normal in all cases.

of the basic coagulative defect of the blood. It is high time therefore for the clinician as well as the investigator to recognize the limitation of the coagulation time.

It should be noted that the second patient with a platelet count of 29,000 showed a higher prothrombin conversion than the first who had a platelet count of 80,000. This suggests that a quantitative difference in the functional activity of platelets may occur. Glanzmann<sup>5</sup> applied the term thrombasthenia to a condition in which platelets were normal in number, but deficient in function. His concept has remained theoretical because of the lack of experimental means to demonstrate changes in the activity of plate-

lets; (2) Clot retraction is characterized by a relatively long latent period followed by an accelerated phase and protracted completion; (3) Within a wide range in the number of platelets no significant change in coagulation time can be observed; (4) As the number of platelets is diminished the speed of prothrombin consumption is decreased, but within limits the final amount of prothrombin converted approximates a fixed value; (5) Below a critical number of platelets (which varies in different bloods) the consumption of prothrombin stops after a relatively short time. This suggests that plasma contains an agent that inactivates the platelet enzyme; (6) In

thrombocytopenic purpura of sufficient severity, the consumption of prothrombin may be markedly diminished. This constitutes important evidence that a serious defect in coagulation is present which has heretofore been unrecognized because it is masked by a normal coagulation time.

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# AN ELECTROPHORETIC ANALYSIS OF THE PLASMA PROTEINS IN THE AGED

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We have reported elsewhere<sup>8,9</sup> the fact that evidence of liver dysfunction was found in apparently normal individuals over 65 years of age when the hepatic function was tested by 5 different liver function tests. After a 5-year interval, a reinvestigation of the hepatic function in the aged was undertaken with substantially the same findings.<sup>10</sup> A chemical determination of the total plasma proteins and the albumin-globulin ratio by fractionation with sodium sulphate, however, failed to show any significant deviation from the commonly accepted normals.<sup>3,4,5</sup> It was therefore thought of interest to

investigate the partition of the plasma proteins in a group of apparently normal individuals by electrophoretic analysis, since the sensitivity of the method is such that any qualitative as well as quantitative variation from the normal could be detected. To the best of our knowledge, no such study has thus far been reported.

**Experimental Method.** The subjects whose plasma proteins were studied comprised 21 apparently normal individuals whose age range was between 70 and 95 years. Eleven were males and 10 were females. All were ambulatory and were on the usual institutional dietary regime which has been shown to be adequate in nutritional elements.<sup>11</sup>

TABLE 1.—ELECTROPHORETIC PATTERNS OF PLASMA OF THE SUBJECTS UNDER INVESTIGATION  
(Figures represent percentage of total proteins)

No.	Age	Sex	Alb.	Alpha Glob.	Beta Glob.	Gamma Glob.	Fib.	Total Glob.	A/G
1.	70	M	61.9	6.9	16.2	10.6	4.4	33.7	1.83
2.	79	F	55.0	7.1	18.6	12.2	7.1	37.9	1.45
3.	85	F	59.0	6.2	10.0	14.0	10.9	38.2	1.95
4.	89	F	57.6	6.3	14.6	14.6	6.3	35.5	1.62
5.	70	M	59.3	7.3	14.6	12.2	6.5	34.1	1.74
6.	76	F	50.7	10.0	15.7	12.9	10.7	38.6	1.31
7.	73	M	50.7	8.0	17.4	13.4	8.8	42.2	1.18
8.	80	F	50.5	9.2	20.6	12.6	7.4	42.4	1.19
9.	81	F	62.4	12.6	8.9	9.9	6.3	31.4	1.99
10.	86	M	52.9	9.0	10.3	13.0	9.7	38.3	1.38
11.	71	F	55.2	7.8	18.2	13.0	5.8	39.0	1.42
12.	76	F	58.1	13.5	11.5	10.8	6.1	35.8	1.62
13.	77	M	53.2	12.6	9.8	16.1	8.4	38.5	1.38
14.	95	M	55.3	7.4	14.7	15.3	7.4	37.4	1.43
15.	76	F	57.8	9.7	12.2	13.0	7.3	34.9	1.65
16.	83	M	56.5	13.6	7.1	13.6	9.3	34.3	1.65
17.	78	F	50.0	12.0	14.7	14.7	8.7	41.4	1.21
18.	80	M	52.6	9.0	16.5	14.3	7.5	39.8	1.32
19.	76	F	59.3	5.9	14.5	15.8	4.6	36.2	1.64
20.	94	M	48.6	6.1	23.0	16.2	6.1	45.3	1.07
21.	70	M	47.5	9.4	16.9	15.0	11.3	41.3	1.15

The plasma was obtained with the patient in the fasting state. Sodium citrate was employed as an anti-coagulant and the cells were immediately removed after the specimen was centrifuged. The plasma was stored in a frozen state until it was ready for processing. The plasma was thawed at 0°C, diluted 1 to 4 with a buffer which was 0.02M with respect to phosphate ion, and 0.15M with respect to sodium chloride, and had a pH of 7.6. The diluted plasma was then placed inside a dialyzing membrane and dialyzed against the phosphate buffer for 8 hours, after

**Results.** The experimental findings are presented in Table 1. It may be seen from this Table that the albumin ranged from 47.5 to 62.4% of the total proteins, with an average of 55%; the globulins, exclusive of the fibrinogen, ranged from 31.4 to 45.3% of the total, with a mean of 37.9%. The fibrinogen ranged from 4.4 to 11.3%, with an average value of 7.7%. This gave an A/G ratio between 1.07 and 1.99, with a

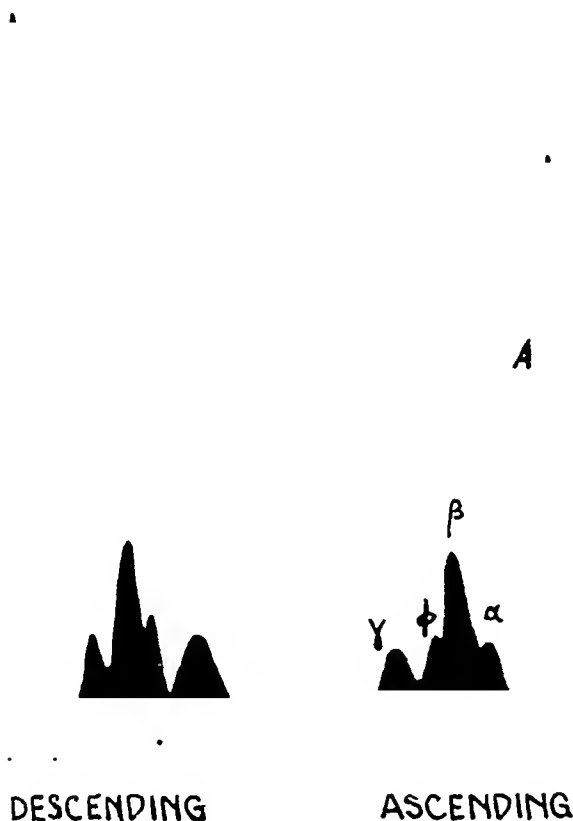


FIG. 1. Curve 1.—Tracing of the electrophoretic pattern from Subject 1.

which the buffer outside the membrane was replaced by 2 liters of fresh buffer solution, and the dialysis carried out for an additional 16 hours. This dialysis was done at a temperature of from 0 to 2°C.

The electrophoresis was carried out for approximately 3½ hours in a Klett apparatus, in a 2° water bath. Both ascending and descending Schlieren patterns were obtained. The albumin, alpha, beta, and gamma, globulin fractions were computed from the descending patterns and fibrinogen was measured on the ascending portion. This procedure was followed for purely practical purposes.

mean value of 1.4. There was no significant difference between the values for males and females. In 12 of the 21 subjects, or 57%, the albumin globulin ratio was less than 1.5. Nine of the subjects or 43%, had plasma albumin values which were less than 55% of the total proteins. In 16 of the 21 individuals, or 76%, the total globulin was more than 33% of the total proteins.

The globulin fractions in the 21 subjects were as follows: (Table 1): The

alpha globulin ranged from 5.9 to 13.6% of the total protein with an average of 0.092. The beta globulin was 7.1 to 23% of the total protein with a mean of 0.148. In 14 of the 21 individuals or 67%, the beta globulin was above 14%, which was found to be the upper level in healthy young adults. The gamma glob-

dividuals. For this reason it is necessary to compare our findings with the results of those made in younger groups.

In Fig. 1, Curve 1, which represents a tracing of the electrophoretic pattern from Subject 1, compares favorably with the normal electrophoretic pattern which was found by other investi-

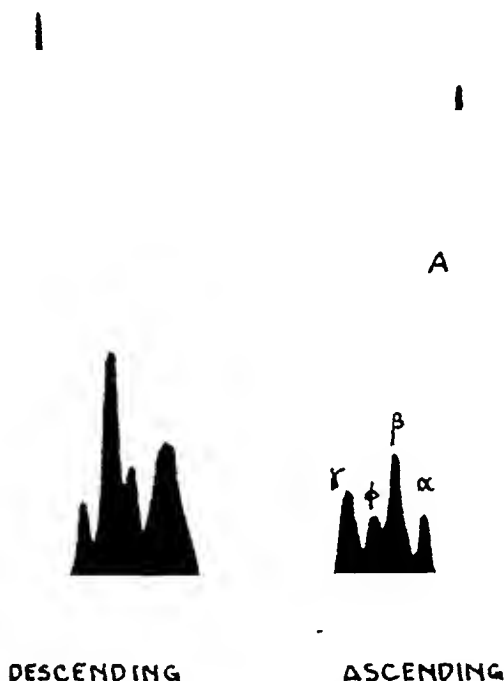


FIG. 2. Curve 8.—Tracing of the electrophoretic pattern from Subject 8.

ulin fraction ranged from 9.9 to 16.2% of the total protein, with an average of 0.138.

**Discussion.** Various investigators<sup>1,6</sup> have undertaken to fractionate the plasma proteins in young normal adults and in patients suffering from various diseases, but to the best of our knowledge, no such study has been made of the plasma of the normal aged in-

gators. In this curve, there was found an A/G ratio of 1.83, which is a normal value. On the other hand, in the curve obtained for Subject 8, with an A/G ratio of 1.19, the pattern (Fig. 2) is somewhat different. It may be noted that the area under the curve for the globulin fraction is greater than that shown in Curve 1. In Subject 20, who had a A/G ratio of 1.07, the curve

TABLE 2.—COMPARISON OF RESULTS IN THIS STUDY WITH THOSE REPORTED FOR YOUNG HEALTHY ADULTS

Author	Alb.	Alpha Glob.	Beta Glob.	Gamma Glob.	Total Glob.	Fib.	A/G.
Martin <sup>7</sup>	0.58	0.095	0.11	0.10	0.31		1.5
	to	to	to	to	to		to
	0.62	0.14	0.14	0.14	0.42		1.9
<sup>a</sup> Leutscher <sup>6</sup>	0.63	0.07	0.13	0.13	0.38	0.06	1.7
<sup>a</sup> Moore and Lynn <sup>1</sup>	0.67	0.07	0.13	0.12	0.33		1.94
<sup>a</sup> Rafsky, Newman and Krieger	0.55	0.092	0.148	0.138	0.38	0.077	1.45

<sup>a</sup> Average values.

showed a more abnormal pattern (Fig. 3).

In Table 2 there is shown the average result for the plasma fractions reported by several investigators, as compared with the values found in this study for the older group. It will be noted that the mean albumin percentage found in this study is well below the mean albumin value reported by others. The total globulin is correspond-

globulin complex contains most of the lipid carrying protein of the blood stream. With this in mind, the increase in the beta globulin fraction in the majority of apparently normal aged subjects becomes understandable, since it has been shown in a previous report<sup>9</sup> that the total cholesterol is elevated in most of the individuals past the age of 65 years.

The gamma globulins of the majority

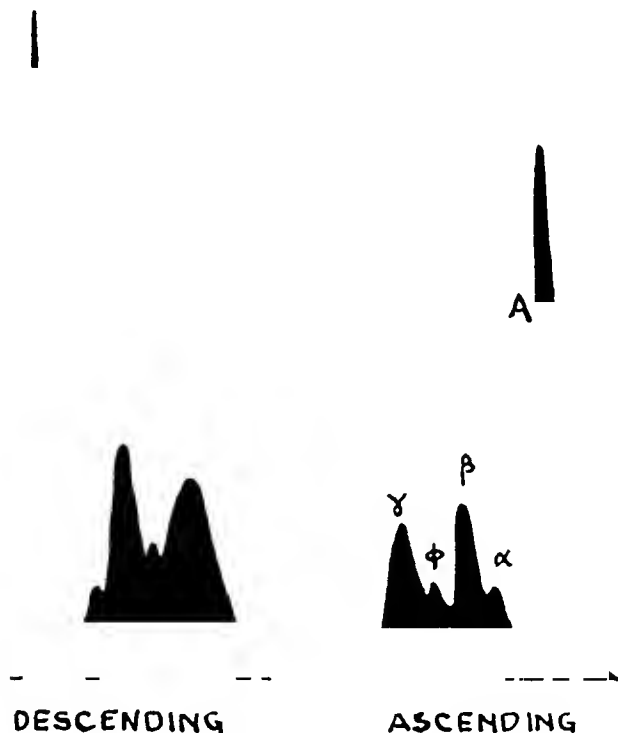


FIG. 3. Curve 20.—Tracing of the electrophoretic pattern from Subject 20.

ingly higher, with the result that there is an A/G ratio lower than that reported by others for younger healthy adults.

In Fig. 4 are shown the frequency distributions for the various protein fractions. They appear to follow, on the whole, the normal distribution curve.

The average value for alpha globulin in the plasma of the subjects in this study were within the normal levels reported by other investigators. In 67% of our individuals the beta globulin were increased. It has been shown by Blix, Tiselius and Svenson<sup>2</sup> that the beta

of the subjects appears to be within the normal limits reported by others for younger groups. This is not without possible significance, since the gamma globulins contain the antibodies to various antigens with which the individual has come in contact during his or her lifetime. It might be postulated that the subjects in our group, having been exposed to various diseases over a longer period, should have a greater total amount of antibody reflected by a rise in gamma globulins. However, investigations of certain antibodies (heterophile, febrile and complement titers) by Rafsky, Silberstein

and Newman,<sup>12</sup> have shown that in most cases, normal or even lower than normal titers of antibodies are present in the sera of normal aged subjects.

**Summary.** 1. An electrophoretic analysis of the plasma proteins was made in a group of 21 apparently normal aged subjects.

2. In 12 of the 21 subjects, or 57%, the albumin-globulin ratio was less than 1.5.

3. In 9 of the 21 subjects, or 43%, the plasma albumin was less than 55% of the total protein.

4. In 16 of the 21 subjects, or 76%, the total globulin was more than 33% of the total plasma proteins.

5. In 14 of the 21 subjects, or 67%, the beta globulin was higher than the upper normal levels reported for healthy young adults.

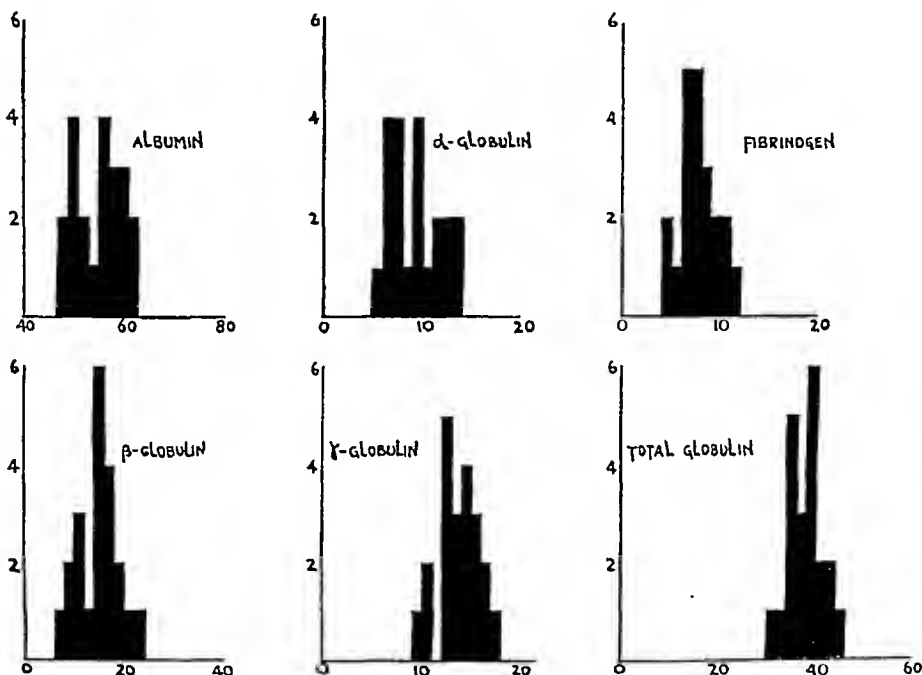


FIG. 4.—Frequency distribution for percentages of various fractions.

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# THE ERYTHROCYTE SEDIMENTATION RATE IN BRUCELLOSIS\*

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ACTIVE cases of human brucellosis are not readily detected. Therefore, there is need for any clinical or diagnostic procedure that will aid in the recognition of the disease. It has been stated that brucellosis may at times be differentiated from other infections because in them the sedimentation rate of erythrocytes is usually shortened<sup>2</sup>. Initial clinical studies in this clinic supported this statement, but with the accumulation of more data on bacteriologically proved acute and chronic cases of brucellosis, the sedimentation rate has been found to be of practically no aid, diagnostically.

**Material and Methods.** The findings in this report are based upon investigations in 43 human cases of brucellosis. Thirty-nine of the cases were due to *Br. abortus*, two were caused by *Br. suis*, and two by *Br. melitensis*. Fourteen of the patients had an illness of less than 3 months in duration and were regarded as acute cases, while 29 of the patients had been chronically ill for periods of 3 months to 10 years. Seven of the 35 patients, all chronic cases, had demonstrable localizing complications which included bacterial endocarditis, spondylitis, meningitis and a pericholecystic abscess. The Westergren method for measuring the sedimentation rate of erythrocytes was used in which the upper limit for normal males is 10 mm. in 1 hour, and 15 mm. in 1 hour for females.

**Results.** The results of the sedimentation rates were correlated with the duration of the disease, the severity of the disease, the presence of complications and the presence or absence of fever.

**THE SEDIMENTATION RATE IN ACUTE BRUCELLOSIS.** Fourteen cases of acute brucellosis are included in this report. It is of interest that in 9 cases the rates were accelerated, and normal in the other 5. The rate did not appear to be related to the severity of the disease. Two laboratory workers became infected with *Br. melitensis* with a demonstrable bacteremia. One individual had very minimal symptoms, which would have been entirely overlooked as being due to brucellosis under normal circumstances, but 4 determinations showed rapid rates. The second person was moderately ill, and has had 2 relapses, and yet the sedimentation rate was normal. The most rapid rate detected in all of the patients occurred in a patient who had been ill for only 3 weeks, and who made a remarkably rapid recovery following therapy with streptomycin and sulfadiazine<sup>3</sup>.

One can only conclude from the observations made in these cases of acute brucellosis that the erythrocyte sedimentation rate is of no value in differentiating the disease from other infectious diseases.

**THE SEDIMENTATION RATE IN CHRONIC BRUCELLOSIS.** A total of 81 determinations were carried out in 29 patients who had had evidence of active disease for 3 months or longer. Normal rates were obtained in only 7 of the 29 subjects. The presence or absence of an accelerated rate had no relationship to the

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severity of the illness in this group of patients. Included in this group is a father and his son with chronic disease due to *Br. abortus*. The former was moderately ill, and his sedimentation rates remained normal. The son, on the other hand, was afebrile, though bacteremic, and had very little in the way of symptoms, and yet his rates were accelerated.

caused by *Br. abortus*, one had normal rates, while the other had rapid rates. The patient having the pericholecystic abscess due to *Br. suis* had rapid rates whereas the patient with meningitis due to *Br. abortus* had normal rates. In this small group of patients, then, with serious complications, the sedimentation rates were not uniformly elevated. The sedimentation rate would not ap-

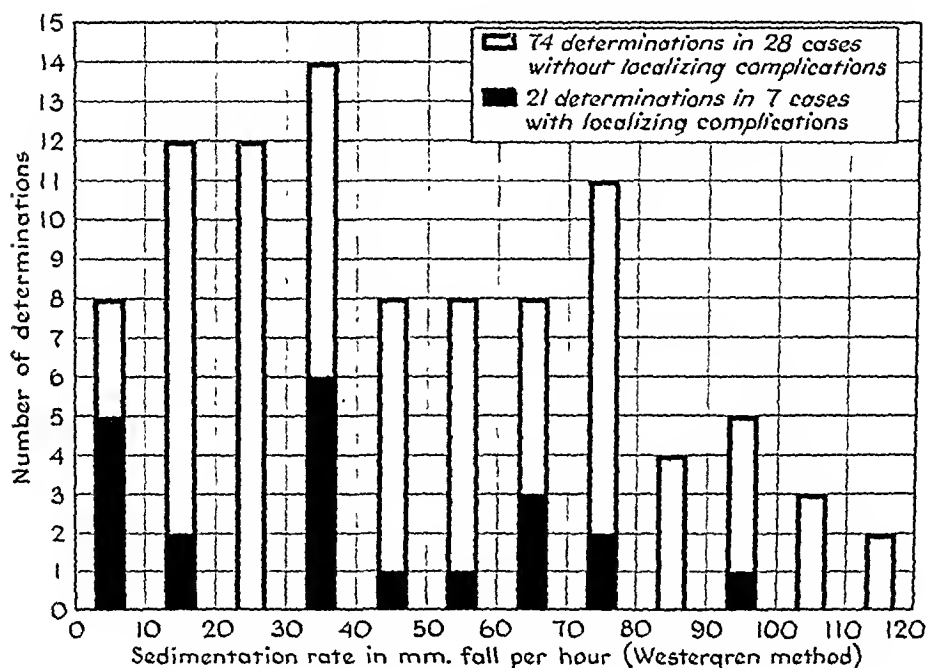


FIG. 1.—Frequency distribution of sedimentation rates in 35 cases of bacteriologically proved brucellosis: 95 determinations.

The sedimentation rate in chronic cases of brucellosis is of little practical value in the differential diagnosis of the disease.

**THE SEDIMENTATION RATE IN CASES WITH DEMONSTRABLE COMPLICATIONS.** Complications were observed only in 7 patients having the chronic form of the disease and included subacute bacterial endocarditis, spondylitis, meningitis and a pericholecystic abscess with abscesses of the liver. Two patients having subacute bacterial endocarditis due to *Br. abortus* had accelerated rates. Of 2 individuals with spondylitis

appear too helpful in ascertaining if complications were present.

The foregoing data have been presented graphically in Fig. 1, along with the frequency distribution of sedimentation rates in a total of 35 cases of proved brucellosis.

**THE RELATIONSHIP OF THE SEDIMENTATION RATE TO FEVER.** A total of 95 determinations of the sedimentation rates was made in 35 proved cases, 7 of them with localizing complications previously described, with relation to the temperatures of the patients at the time the tests were made. The informa-

tion is presented graphically in Fig. 2. There was no direct relationship observed between the height of the fever and the rapidity of the sedimentation rate.

**PROGNOSTIC VALUE OF THE SEDIMENTATION RATE IN BRUCELLOSIS.** Although the sedimentation rate is of little diagnostic value in brucellosis, the proce-

recover completely or who had relapses had consistently elevated rates. In the latter group of cases, the rapid sedimentation rates occurred in individuals who were afebrile and abacteremic, yet who were ill.

**Discussion.** The observations recorded in this paper indicate quite clearly that the erythrocyte sedimen-

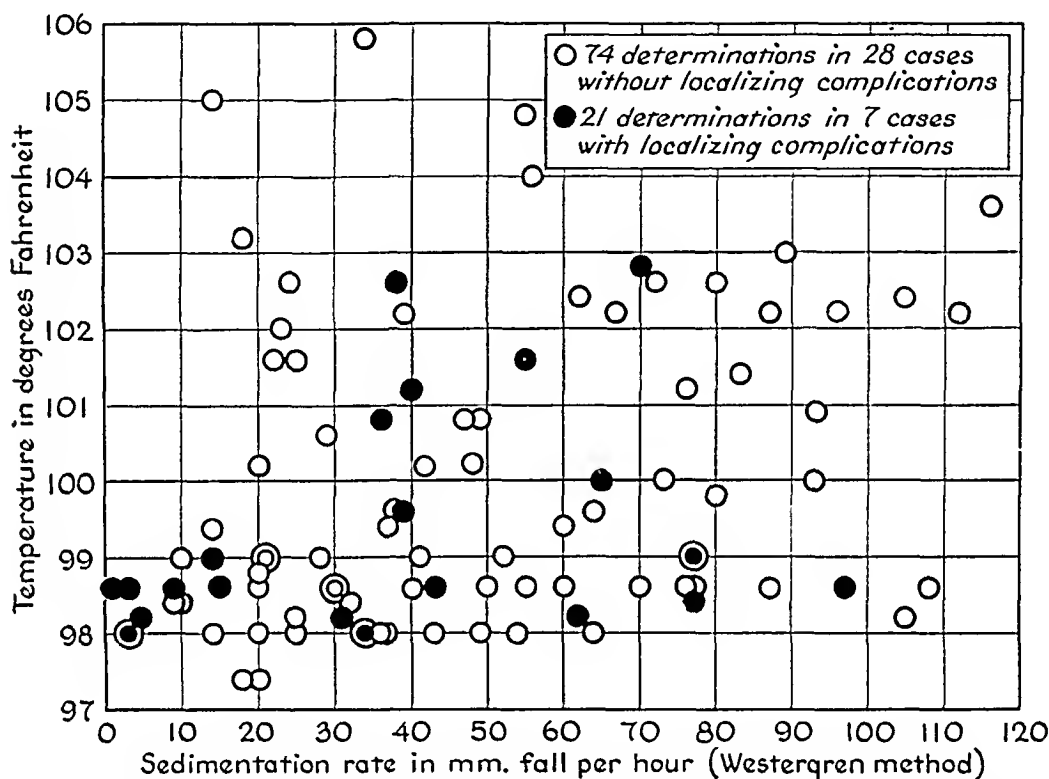


FIG. 2.—Comparison of sedimentation rate and fever in 35 cases of bacteriologically proved brucellosis. 95 determinations.

ture may be of aid in interpreting the clinical course of the patient. The sedimentation rate has been helpful in ascertaining whether active disease is still present in patients who have recovered symptomatically. Although further investigations are necessary, and patients will have to be followed for a number of years, it has been observed on several occasions that as the patient assumed a state of normal health, either as a result of specific treatment or spontaneously, the sedimentation rate approached or became normal. Conversely, the patients who did not

tation rate is of no practical value in differentiating active brucellosis from other infectious diseases. Patients quite ill with a chronic form of the disease may have normal rates, even in the presence of complications. Another chronic infectious disease with similar findings is tuberculosis.<sup>1</sup> Patients with extensive pulmonary tuberculosis may have normal sedimentation rates. Active rheumatic fever is another condition where normal rates may be obtained.

The sedimentation rate may be of definite aid from a prognostic point of

view in brucellosis; that is, in patients having an accelerated rate, although they are symptomatically well, there exists more of a possibility for a clinical relapse than in individuals who have recovered simultaneously with a return of the sedimentation rate to normal values. Similar observations have been made in patients with chronic disease such as tuberculosis and rheumatic fever.

Summary. 1. The erythrocyte sedimentation rate was evaluated in 43 pa-

tients having bacteriologically proved acute or chronic brucellosis. The test was found to be of little practical value in differentiating brucellosis from other infectious diseases. Normal or accelerated rates had no definite relation to the duration or severity of the illness.

2. Sedimentation rates appear to be of some prognostic help in ascertaining the presence or absence of active disease in patients who have recovered symptomatically from the disease. Persistent rapid rates appear to be associated with continued active disease.

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# PROGRESS OF MEDICAL SCIENCE

## SURGERY

UNDER THE CHARGE OF

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## CARCINOMA OF THE FEMALE BREAST

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ALTHOUGH the treatment of carcinoma of the breast has undergone no radical transformation within the past few years, the disease has taken on new significance by reason of certain related developments. First, the number of patients seeking medical advice for breast symptoms has increased as a result of the concern aroused by the educational campaign of the American Cancer Society, the Public Health Service, and other agencies. The layman is becoming increasingly cancer conscious, and many women who, 10 years ago, would not have known what a lump in the breast signified or how to locate it are now thoroughly conversant with the symptoms of carcinoma and are seeking medical attention at the slightest suggestion of trouble. This means that there is now a greater opportunity to reduce the high mortality from breast cancer through early diagnosis and early treatment.

A second development which has important bearing on breast cancer is

the experimental work being performed on animals. A large part of general cancer research is now directed toward mammary cancer, and recently there have been opened up new avenues of approach which may prove applicable to the problem of the control of human breast cancer. The physician will find it worth while to review briefly the existing knowledge about this important disease.

INCIDENCE. In 1946 carcinoma of the breast caused 17,500 deaths in the United States, a crude death rate of 12.5 per 100,000 persons.<sup>18</sup> Cancer of the breast is not as lethal as cancer in many other parts of the body. Only one-fifth of patients with breast cancer die within a year of diagnosis as compared to an average of one-third of all types of cancer.<sup>20</sup> Thus the prevalence of mammary cancer among the living is even more striking than its high death rate. Dorn,<sup>21</sup> in 1944, estimated on the basis of the urban white population that there were 108 patients

with carcinoma of the breast per 100,000 persons. Approximately 99% of all breast carcinoma occurs in females. Recent morbidity data from New York State indicate that the breast is by far the most frequent site of cancer in women, being almost twice as common as cancer of the cervix and 3 times as common as cancer of the stomach.<sup>14,36</sup> In 1946 the number of women dying from breast cancer was larger than from any other type of cancer, with the exception of cancer of the digestive system.<sup>18</sup>

The death rate from cancer of the breast increased from 10.7 per 100,000 population in 1936 to 12.5 in 1946, but these are crude death rates and do not allow for the ageing of the population during the period.<sup>36</sup>

**ETIOLOGY OF CARCINOMA OF THE BREAST. Animal Experimentation.** A tremendous amount of work has been done on the genesis of mammary tumors in the experimental animal, especially the mouse. The work was recently reviewed by Shimkin.<sup>35</sup> The development of mammary cancer in the mouse appears to be controlled by the following 3 factors: (1) its genetic constitution, (2) a milk factor, and (3) hormonal stimuli.<sup>50,55</sup>

For many years strains of mice with a high incidence of breast cancer due to a gene or chromosomal factor have been produced by inbreeding experiments. In 1936 Bittner<sup>9,10</sup> discovered that the development of mammary carcinoma in mice was partly dependent on another factor, extrachromosomal, in the mother's milk. By suckling young females of a low tumor strain on mothers of a high tumor strain, the incidence of mammary carcinoma was increased. Bittner's work has been confirmed by many investigators.<sup>7,39</sup> By this method Haagenensen and Randall<sup>39</sup> recently induced mammary cancer in 76% of the females of a strain of mice in which there was

no mammary carcinoma among control animals. They found that as little as 0.2 cc. of milk could induce cancer. The responsible agent in the milk has not yet been identified but has been postulated to be a virus. The milk factor was not found in whole blood in significant concentrations.<sup>33</sup>

Lacassagne,<sup>58</sup> in 1932, produced breast carcinoma in male mice by the injection of large doses of estrogens. His work has been greatly extended.<sup>29,86,90,95</sup> Geschickter<sup>29</sup> reported the production of mammary cancer in 100% of nonsusceptible rats, male or female, by prolonged administration of estrogens. Shimkin and Wyman<sup>56</sup> found the carcinogenic dose for male mice within the ranges of concentration elaborated by the normal female of the species. The fact that carcinoma is produced not only by the naturally occurring steroids but also by synthetic estrogens with a different chemical structure suggests that estrogens are not directly carcinogenic but that they stimulate the tissues to provide a medium suitable for the development of cancer.<sup>95</sup>

It is difficult to assess the relative importance of the three factors—heredity, milk factor, and hormonal stimulation—because of the unsolved problems involved in an attempt to measure one independently of the others. That they do work independently is suggested by the variations which occur in the mouse's mammary gland depending on which factor is predominating.<sup>54</sup>

Mammary cancer has also been induced in mice by the cutaneous and intraperitoneal administration of methyl cholanthrene.<sup>57,79</sup>

**Etiologic Factors of Importance in the Human.** Heredity, the milk factor, and hormonal stimulation have not been proved to be of primary significance in the etiology of human cancer. In the human, hereditary factors are

probably only of importance as regards organ specificity.<sup>14,23,71,88</sup> McDonald<sup>71</sup> found that in relatives of patients with carcinoma of the breast the incidence of mammary cancer was 3 times that expected.

No evidence has yet been found of the operation of the milk factor in the human. Macklin<sup>72</sup> suggested that an attempt be made to trace a group of women whose mothers died in childbirth and who were not nursed by a wet nurse. A low incidence of carcinoma of the breast in such a group would suggest a direct relationship. As yet the available facts do not justify the recommendation that women with a family history of cancer should not nurse their young,<sup>14,72</sup> although this has been suggested.<sup>44</sup>

In 1944 Nathanson<sup>74</sup> summed up the evidence for the hormonal causation of carcinoma of the breast as follows: "Hormones may possibly be the direct cause of malignant change in the breast, either from an excess stimulation or as the result of an atypical metabolism. As yet there is not concrete evidence to prove this. It is likely that they merely prepare a substrate upon which another agent may act." For many years estrogenic hormones have been given to large numbers of women for therapeutic purposes, but only rare reports have appeared which would indicate that carcinoma of the breast might have been caused by such administration.<sup>6,9,80</sup> In these cases the evidence that carcinoma was produced by estrogens was not conclusive.

Two recent case reports suggest a causal relationship between carcinoma of the male breast and hormones. One man developed carcinoma following ingestion of 1,097 mg. of diethylstilbestrol over 489 days<sup>1</sup>; another had carcinoma of the breast associated with chorioncarcinoma of the testis.<sup>65</sup>

The results of animal experimentation would seem to warrant Chase's

admonition<sup>14</sup> that "estrogens should not be given to any woman in amounts greater than normally occurring; and none at all to women with a family history of carcinoma, especially of the breast; and none to a woman operated on for a breast tumor, before or after operation."

Childbearing and nursing apparently decrease the likelihood of the development of breast cancer.<sup>2,14,22,71,78,83</sup> This has given rise to the stagnation theory of causation. Adair<sup>2</sup> reported that only 8.5% of patients who developed mammary cancer gave a normal nursing history, whereas 80% of a control group of healthy women had nursed their children normally. For prophylaxis against breast cancer he advised that the mother nurse her children unless definite contraindications were present. If the milk factor proves to be effective in the human and if nursing is discouraged, the mother's chances of developing cancer may be increased in order to decrease those of the child.

An attempt was made to determine the effect of fertility on the age at which cancer of the breast occurs by a detailed study of 201 women treated at the Hospital of the University of Minnesota.<sup>73</sup> It was found that the average age of occurrence of breast cancer was the same for sterile women, those with low fertility, and those with a large number of pregnancies.

Carcinoma of the breast is most common in middle life.<sup>76</sup> The peak of the age incidence is between 46 and 48 years and the median age, 52. One-third of the patients are from 45 to 55 years of age.

The presence of certain benign lesions in the breast has been thought to increase the likelihood of cancer. It is probable that intraductal papilloma more than any other breast lesion predisposes to the development of cancer.<sup>33</sup> Exhaustive studies have been made to determine the relation of chronic

cystic mastitis to carcinoma of the breast, but the subject is still controversial. The studies of Warren<sup>98,99</sup> and Logie<sup>62</sup> suggest that there is a causal relationship. Warren's data indicate that the breast cancer attack rate for women from 30 to 49 years of age with chronic cystic mastitis is 11.7 times the rate for the Massachusetts female population. Other reports have stated that most types of chronic cystic mastitis are not precancerous.<sup>26,30,61</sup> Geschickter<sup>30</sup> stated that only in adenosis is there a significant predisposition to malignancy. It appears that the causal relationship, if it exists, is tenuous. There is general agreement that the danger of cancer is not great enough to warrant simple mastectomy in this condition for prophylactic reasons.<sup>26,30,91,98</sup>

**PATHOLOGIC HISTOLOGY.** Foote and Stewart,<sup>27</sup> recognizing that no generally accepted classification of breast carcinoma existed, recently published the classification used at the Memorial Hospital in New York City:

#### HISTOLOGIC CLASSIFICATION OF CARCINOMAS OF THE BREAST

##### I. PAGET'S DISEASE OF THE NIPPLE.

II. CARCINOMAS OF MAMMARY DUCTS. (a) *Noninfiltrating tumors*: 1, Papillary carcinoma; 2, Comedo carcinoma.

(b) *Infiltrating tumors*: 1, Papillary carcinoma; 2, Comedo carcinoma; 3, Carcinoma with productive fibrosis; 4, Medullary carcinoma; 5, Colloid carcinoma.

III. CARCINOMAS OF MAMMARY LOBULES. (a) *Noninfiltrating*; (b) *Infiltrating*.

IV. RELATIVELY RARE CARCINOMAS. (a) *So-called sweat gland carcinoma*; (b) *Intracystic carcinoma*; (c) *Spindle-cell carcinoma, "adenosarcoma"*; (d) *Adenoid cystic carcinoma*; (e) *Carcinoma with osseous and cartilaginous metaplasia*; (f) *Squamous carcinoma*; (g) *Malignant variant of fibro-adenoma and cystosarcoma phyllodes*.

It is now generally thought that Paget's disease of the nipple always arises in the mammary ducts and extends to the nipple only secondarily.<sup>15,27</sup>

**PREOPERATIVE DIAGNOSIS.** It may be stated that, in general, the easier the diagnosis of a given cancer of the breast, the less the chance of cure. Skilled observers may be able by a painstaking physical examination to differentiate a small benign from a small malignant lesion in a high percentage of instances.<sup>36</sup> This is probably not possible for most examiners.<sup>25,91</sup> What is most important is the recognition of small and indefinite "dominant lumps" and their subsequent excision for gross and microscopic examination.<sup>89</sup> Small axillary metastases are particularly difficult to recognize preoperatively, and nodes enlarged by benign processes are often mistaken for axillary metastases.<sup>23,91</sup>

In recent years, several types of benign breast lesions have been described which may give all the clinical signs of carcinoma: plasma cell mastitis,<sup>28</sup> granular cell myoblastoma,<sup>40</sup> circumscribed suppurative mastitis,<sup>94</sup> and comedo mastitis.<sup>92</sup> The fact that these lesions often cannot be differentiated from carcinoma by a preoperative examination emphasizes the necessity of biopsy before performing a radical mastectomy.

Low-Beer and his co-workers<sup>63,64,79</sup> of the University of California have recently reported interesting experiments on the diagnosis of breast lesions using radioactive phosphorus ( $P_{32}$ ). Twenty-four or 48 hours before operation tracer doses of radioactive phosphorus were administered intravenously in the form of disodium hydrogen phosphate solution to patients with breast lesions. Skin surface measurements of radioactivity were made with the Geiger-Müller counter. Sixteen of 17 patients with benign breast lesions gave skin surface measurements comparable to those of

normal skin. Of 41 patients with malignant lesions of the breast, all but 7 showed an increase in skin surface measurements of over 25%. These 7 included very small and deeply seated lesions. Benign inflammatory lesions gave greatly increased radioactivity over the infected areas.

Roentgenography of the breast, either with or without injection of opaque material into the ducts, has been recommended as an aid in the diagnosis of breast lesions,<sup>31,59,69</sup> but has not generally been accepted as having much value.

**PROGNOSIS OF THE UNTREATED PATIENT.** In 1946 Wade<sup>97</sup> compiled data from several reports on 777 patients with carcinoma of the breast who had had no treatment whatsoever. The average duration of life from the onset of symptoms was 38.3 months. Spontaneous cure has not been reported. In Daland's series<sup>17</sup> of 100 untreated patients the average duration of life after the onset of symptoms was 40.5 months, and 22% of the patients were alive after 5 years, 9% after 7 years, and 5% after 10 years.

**TREATMENT.** It is generally agreed that our present techniques of treating breast cancer are of real value in the cure of early lesions and are effective in the palliative therapy of advanced disease. In treated patients one can expect a 5 year survival of approximately 40%.<sup>15,41,16,52</sup> The prognosis in cancer of the breast is considerably influenced by the presence or absence of axillary metastases. If the lesion is limited to the breast, approximately 60 to 85% of patients can, with proper treatment, be expected to survive 5 years or more; whereas with axillary node involvement only approximately 25% will live 5 years.<sup>14,30,11,16,17,52,66,69,82,88,91,93</sup> Warren and Tompkins<sup>100</sup> have shown that both the cure rate and the survival time decrease as the extent of axillary metastases increases. Yet treatment is of

value even in far advanced carcinoma of the breast. Wade<sup>97</sup> estimated that even in advanced breast carcinoma radiotherapy, alone or combined with surgery, increased the survival rate by 21.5% at 1 year, 22.5% at 2 years, 10% at three years, 10.5% at four years, and 9.5% at 5 years.

Radical mastectomy remains the treatment of choice in carcinoma of the breast. Little new has been added to its technique. The completeness with which the operation is performed is much more important than the type of operation used. This was emphasized by one study<sup>41</sup> in which the survival rate for radical mastectomy was in direct proportion to the duration of the operation. Not only must operation be complete, but great care must be taken not to implant cancer cells in the operative field, *i.e.* to practice "cancer asepsis".<sup>101</sup> Cancer has been implanted into the donor site when skin grafting has been performed in radical mastectomy.<sup>12</sup> Haagensen<sup>37</sup> has recently described his technique of radical mastectomy which emphasizes the fundamentals laid down by Halsted and Willy Meyer and includes routine skin grafting. The careful undercutting of the skin to the limits of deep removal has been advocated to decrease skin recurrences.<sup>13</sup> Rodman<sup>83</sup> attributed a low incidence of skin recurrences (2.2%) following radical mastectomy to extensive skin removal. For the surgeon who finds it necessary to ligate the axillary vein during radical mastectomy it may be of interest to note that significant edema of the arm did not follow its ligation in 4 instances.<sup>24</sup>

Postoperative lymphedema has been a perplexing problem for surgeons. It is most commonly caused by infection and Roentgen-ray dermatitis.<sup>51</sup> Guthrie and Gagnon<sup>35</sup> have reported an operation for the relief of lymphedema in which several collodion strips are inserted subcutaneously from the arm to the chest and left in place for 3 weeks.



In recent years there has been a tendency to limit the criteria of operability of carcinoma of the breast because of the poor results obtained in far advanced disease.<sup>41,91</sup> Haagensen and Stout,<sup>41</sup> after a careful study of postoperative results, set up the following definite contraindications to operation: 1, distant metastases; 2, inflammatory type of carcinoma; 3, supraclavicular metastases; 4, edema of the arm; 5, intercostal or parasternal nodules; 6, satellite nodules in skin over the breast; 7, carcinoma developing during pregnancy or lactation. They obtained no cures if any of these existed and regarded a patient with any of them as "categorically inoperable".

The following factors were found to signify such a poor prognosis that the presence of any two in a patient was regarded as a contraindication to operation: 1, ulceration of the skin; 2, limited edema of the skin (less than a third of the breast surface); 3, fixation of tumor to chest wall; 4, axillary nodes measuring 2.5 cm. or more in diameter and proved to contain metastases by biopsy; 5, fixation of axillary nodes to skin or deep structures with nodes proved to be metastatic by biopsy.

If these criteria were rigidly observed, the 5 year survival rate would certainly be increased, but some patients would lose the chance of cure.<sup>46,47,52,93</sup> The carcinoma which develops during pregnancy or lactation is not hopeless as shown by reports of long survivals following radical mastectomy in such instances.<sup>46,47,93</sup>

Although most observers have thought surgery to be contraindicated in inflammatory carcinoma of the breast, Meyer, Dockerty and Harrington<sup>73</sup> recently reported 61 patients with inflammatory carcinoma treated by radical mastectomy and postoperative irradiation. Three patients lived more than 5 years after operation, and 1 was alive 9 years after operation.

*Irradiation.* One of the most contro-

versial subjects relative to breast cancer is the value of Roentgen-ray therapy as an adjunct to operation. Preoperative irradiation is rarely used in the United States, but opinions are divided concerning the usefulness of postoperative irradiation. Most observers believe that if the axillary nodes are not involved, postoperative irradiation adds little or nothing to the length of survival.<sup>3,32,34,87</sup> There has been great disagreement as to the value of irradiation when axillary metastases are present. Most writers have advised routine postoperative irradiation if axillary metastases are present,<sup>3,34,45,55, 56,60,66,67,68,77,82</sup> but no very convincing statistical proof of its value has yet been given. Other authorities do not believe it is worth while except for recurrences or metastases.<sup>38,81</sup> As the result of a recent study at Stanford University, Siris and Dobson<sup>87</sup> have eliminated routine postoperative irradiation.

Irradiation is often of striking value for recurrences or metastases. Recent reports have emphasized the increase in survival as well as alleviation of suffering which irradiation affords in far advanced disease.<sup>11,56,84,97</sup>

*Castration.* Because of the possible causal relationship between estrogens and mammary carcinoma, castration has been advocated for the treatment of carcinoma of the breast of women of premenopausal age. Castration has been found to produce temporary improvement in about one-fifth of patients with metastatic carcinoma.<sup>5,43</sup> The greatest effect has been that on bone metastases. There seems to have been little difference in the results whether castration was by irradiation or by surgery. The value of castration as a prophylactic procedure following radical mastectomy is difficult to assess. Adair and his associates<sup>5</sup> advise castration for any young women of premenopausal age shown to have axillary metastases. From a study of 25 patients

treated by radical mastectomy and castration, Horsley<sup>53</sup> has concluded that castration is a valuable adjunct.

*Hormones.* During the last few years both estrogens and androgens have been shown to have beneficial effects on some patients with advanced carcinoma of the breast. Soft tissue manifestations of breast cancer are improved by administration of estrogens in about a third of patients over 60 years of age. A deleterious effect is produced in women who are menstruating.<sup>19,42,49,75</sup>

Androgens may affect metastases from carcinoma of the breast at any age. Testosterone is especially effective against osseous metastases but may affect soft tissue metastases in large doses.<sup>4,48</sup> Neither estrogens or androgens appear to have more than a temporary effect and are probably not as beneficial as Roentgen-ray therapy.<sup>16</sup>

*Summary.* Some of the recent literature concerning carcinoma of the fe-

male breast has been briefly reviewed. Although no radical changes in treatment have occurred, it is logical to expect a decrease in mortality because women with breast lumps are now reporting to physicians earlier. The physician, in turn, must excise all "dominant lumps" for gross and microscopic examination and perform a radical mastectomy if the mass proves to be cancer.

Experimental mammary carcinoma in mice is intimately related to 3 factors: heredity, the milk factor, and estrogens. As yet none of these has been proved to be of primary importance in the etiology of human mammary cancer. The preoperative diagnosis of breast lesions by the use of radioactive phosphorus, now in the experimental stage, is an ingenious new approach which may prove to be valuable.

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# OPHTHALMOLOGY

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## THE EFFECT OF RUTIN IN THE CONTROL OF BLEEDING INTO THE RETINA

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HEMORRHAGIC extravasations into the retina or into the vitreous or both occupy a prominent part in the ophthalmoscopic picture of many of the lesions of the internal eye which have loss of vision as their primary manifestation. In some of these lesions, the bleeding is due either to disturbances in the clotting mechanism of the blood or to defects in the vessel walls, and is the primary factor causing the disturbance of vision. In others, the bleeding is merely a secondary manifestation of an underlying inflammatory or degenerative process in the retina or choroid in which the blood vessels are involved only incidentally. In either event, the control of the bleeding is likely to seem to be the most important factor in the therapy of the retinal lesion. Therefore, the ophthalmologist seizes with avidity on any new drug recommended for this purpose. At first, such drugs are likely to be employed indiscriminately without careful consideration of the mechanism of the hemorrhage or the mode of action of the drug. Gradually, however, the use of the drug is narrowed down to use in those types of cases in which it is at least theoretically rational. This has occurred with rutin and its predecessor, hesperidin.

Hemorrhages in the retina have been noted to be associated frequently with increased fragility of the minute vessels of the skin, particularly in such disease entities as nonthrombocytopenic purpura, hypertension and diabetes mellitus. Various substances, such as citrin, hesperidin and rutin have been advocated for the treatment of such hemorrhagic conditions on the basis of their property of restoring normal capillary integrity in vessels with increased fragility. A rather voluminous literature has appeared recently.

Szent-Györgyi and associates<sup>3</sup> in 1936 first postulated the existence of a substance which they called "vitamin P" (permeability vitamin) on the basis of the action of an extract of Hungarian red pepper and lemon juice in cases of idiopathic or nonthrombocytopenic purpura. This extract was called "citrin" or "vitamin P," and it was suggested that a deficiency of this substance was responsible for the purpuric manifestations. From citrin later was isolated a glucoside, hesperidin, which was first reported in citrus fruits by Lebreton<sup>4</sup> in 1828. Studies of the properties and composition of citrin have shown it to be an impure mixture of hesperidin and eriodictyol, both of which are fla-

vanone glucosides.<sup>24</sup> Mager<sup>35</sup> in 1942 isolated eriodictyol rhamnoside from citrin, and Higby<sup>23</sup> from his study in 1943 of the crude flavone preparations concluded that the eriodictyol glucosides were not the source of vitamin P activity. He further found that pure hesperidin, pure limonin, or pure eriodictyol had no effect, but a substance isolated from crude orange hesperidin, identified as hesperidin methyl chalcone, was found to be active. The flavone glucoside rutin was isolated from buckwheat in 1860 by Schunck.<sup>47</sup> However, the properties of only one of the flavones were little known until Szent-Györgyi reported his findings. Akamatsu<sup>2</sup> in 1931 observed increased action of the frog heart with decreased pulse rate and increased minute volume after administration of such flavones as quercetin, quercitrin, rutin, myricetin, and myricitrin, but noted no other physiologic activity. Rutin is a rhamnoglucoside of the flavonol quercetin, having a chemical structure similar to quercitrin.<sup>58</sup> Couch,<sup>21</sup> in evaluating the capillary action of the various flavones, noted the similarity of the structure of rutin to that of hesperidin. The first studies on human beings were begun in 1942. Hesperidin decreases capillary fragility but has no effect on capillary permeability. Rutin is thought to affect both capillary fragility and permeability.

Abnormality of the capillary walls may be manifested in either or both of two ways: 1. A weak portion of the capillary may rupture with consequent extravasation of blood cells into the tissues, forming a capillary petechia. 2. Permeation of fluid may increase from the capillary into the intercellular spaces. The first abnormality is termed "increased capillary fragility" and the second is called "increased capillary permeability." In the latter condition a larger amount of protein than normal usually is released through the capillary walls. The mechanism of these disturbances is not entirely understood; but, as noted by Peck and Copley,<sup>41</sup>

various physiologic alterations may be the basis for the pathologic manifestations. It may be that there is increased hyaluronidase activity tending to liquefy the pericapillary supporting tissue which contains hyaluronic acid. On the other hand, there may have been damage to the endothelium, resulting in inhibition of production of the intra-endothelial cement substance which may act as a protective coating for the lining of the capillary. Or there may be changes in the pericapillary elastic tissue as a result of which its cushioning effect is impaired to such a degree that application of pressure will cause rupture of the endothelium. Peck and Copley noted that this diversity of physiologic and pathologic possibilities may be responsible for the successful treatment of increased capillary fragility in one disease whereas the same treatment is ineffective in another disease in which the status of the capillaries is apparently similar.

The determination of capillary fragility is made usually by a positive pressure method, either the original supradiastolic technic of Rumpel-Leede or the infradiastolic technic of Göthlin.<sup>47</sup> The majority of recent authors seem to prefer the latter. For testing capillary permeability, the observation of changes in lymph flow by use of vital dyes, such as patent blue V injected intradermally, as originally devised by McMaster,<sup>33</sup> and successfully employed by Griffith and Lindauer,<sup>20</sup> is simple and adequate. Peck and Copley<sup>41</sup> thoroughly reviewed the various methods of testing for capillary abnormalities and gave a complete bibliography of this subject.

Capillary fragility has been found to be elevated in a host of conditions. Diem<sup>7</sup> tested capillary resistance of more than 500 patients by the negative pressure (suction) method of Hecht and found a lowered resistance in minor infections and intoxications, extremely low resistance in polyarthritis, moderate lowering in epidemic

hepatitis, glomerulonephritis, hepatic cirrhosis, gastric and duodenal ulcers, scarlet fever, multiple sclerosis and diabetes mellitus. A lowered content of vitamin C in the blood causes an increase in capillary fragility in scurvy.<sup>1</sup> This responds to the administration of ascorbic acid, but much more readily to combined treatment with ascorbic acid and vitamin P (citrin, hesperidin and rutin). However, Scarborough<sup>45</sup> stated that increased fragility of the capillary walls must be regarded as evidence of a deficiency of vitamin P. He described two forms of subcutaneous bleeding as a result of nutritional deficiency: (1) that caused by a deficiency of ascorbic acid, in which capillary resistance may or may not be low, but in which large ecchymoses involve the subcutaneous tissue and muscles, and (2) that caused by a deficiency of vitamin P, in which small petechiae are found in the skin. He stated that vitamin P alone does not control the large subcutaneous hemorrhages, anemia and general malnutrition characteristic of the scorbutic state, but these respond readily to large doses of ascorbic acid. But, he stated, vitamin P does benefit a lowered capillary resistance, if present in a case of scurvy.

Increased capillary fragility has not been reported in any individuals who are healthy. Cutter and Marquardt<sup>6</sup> stated their belief that all chronic diseases, such as rheumatic heart disease, hypertensive cardiovascular disease, diabetes mellitus and so forth, predispose to increased fragility. They found the highest degree of increased capillary fragility, as seen by capillary ruptures in the nail beds, in patients whose systolic blood pressure exceeded 200 mm. of mercury. Other conditions, associated with increased capillary fragility reported in the literature, are pulmonary hemorrhage, heart block, nuclear lesions of the eighth nerve,<sup>49</sup> irradiated tissues,<sup>19</sup> frostbite,<sup>13</sup> and toxic

reactions due to sulfadiazine, gold salts and aspirin.<sup>49</sup>

That there is a high incidence of increased skin capillary fragility in hypertensive cardiovascular disease is well shown by the work of Griffith.<sup>13</sup> He tested 1,600 patients whose blood pressures were elevated and found that 19% had increased fragility of the capillaries and an added 11% had increased permeability of the capillaries. He noted further that 10% of those with abnormality of the capillaries had an attack of apoplexy within 16 months, whereas only 1.9% of those with normal capillaries had such an attack. Furthermore, 9% of those with damaged capillaries had subsequent retinal hemorrhages, while these were present in only 2% of those with normal capillaries. He found that 73% of the patients who had retinal hemorrhages had increased capillary fragility or permeability. Shanno and his associates<sup>50</sup> found that 75% of a series of 79 individuals who had hemorrhages in the retina associated with hypertension, diabetes mellitus or both had increased capillary fragility or permeability.

Since the publication of the results in the first group of patients with increased capillary fragility and permeability who were treated with rutin by Griffith, Couch and Landauer,<sup>21</sup> there have been many reports on its effects on various conditions. Favorable results have been reported in the treatment of gross hematuria from congenital polycystic kidneys,<sup>11</sup> of experimental frostbite,<sup>13</sup> of increased capillary fragility produced in rats by irradiation,<sup>19</sup> and of gastro-intestinal bleeding in hereditary hemorrhagic telangiectasia.<sup>27</sup> Madison and Polile<sup>34</sup> stated that in 88% of 173 reported cases of purpura of various types the fragility decreased under treatment with rutin. These authors presented 14 cases of purpura in which this type of treatment gave questionable to excellent results. Stocker,<sup>52</sup> after investigation of the effect of rutin on the blood-aqueous

barrier, concluded that rutin causes only slight tightening of the barrier in normal rabbits, but when physostigmine is instilled into the conjunctival sac of a previously rutinized animal the increase in permeability of the barrier is much less than that which ordinarily follows instillation of physostigmine. McManus and Landrigan<sup>32</sup> treated 10 patients who had increased capillary fragility and 5 normal patients with from 20 to 40 mg. of rutin 3 times daily for 4 weeks with irregular results. They concluded, therefore, that rutin was ineffective in this group, but showed no toxic effects.

Concerning the treatment of the increased capillary fragility of patients with hypertensive cardiovascular disease, there have been several excellent papers, particularly those of the Griffith, Shanno, Lindauer group. This study is well summarized by Griffith.<sup>13</sup> Repeated studies for periods up to 48 months (average 16 months) were made on 189 patients with elevated blood pressure and with defects of the capillary walls. These patients were given initially 60 mg. of rutin each day. Tests were repeated every 6 weeks when results showed abnormal conditions and every 3 months when results were normal. The dosage of rutin was increased by 20 mg. per day whenever the tests indicated abnormalities. For 72% of the patients 60 mg. daily was sufficient to maintain capillary integrity; for 87% 80 mg. or less daily was sufficient, but 13% required varying amounts up to 400 mg. per day. In 75% of the cases results of tests became constantly normal, but in 25% they were intermittently normal. In the latter group, all but 6% of the patients were irregular in attendance for treatment and follow-up. In 16 months of observation it was found that apoplexy occurred in 1.5% of the patients in the treated group who had normal results of tests and in 9% of the group who had received irregular treatment and had had only transient periods of

normal capillary resistance. The incidence of retinal hemorrhages in these two groups was the same as the incidence of apoplexy, but the retinal and cerebral lesions did not occur necessarily in the same individuals. Among 52 persons, having retinal hemorrhages, further hemorrhage occurred in 44%, 5.7% of this group had normal capillaries and 38.3% had an abnormal condition of the capillaries under treatment. It was found that treatment with thiocyanate increased the capillary permeability and capillary fragility in 8% of those treated. Madison and Pohle<sup>34</sup> reported questionable results from rutin therapy of 1 hypertensive patient with retinal hemorrhages. Goedbloed<sup>16</sup> described a patient whose petechial index returned to normal in 8 weeks with concomitant disappearance of retinal hemorrhages. Zfass<sup>60</sup> reported 4 cases of hypertensive cardiovascular disease with rapid clearing of retinal hemorrhages in 3 when increased capillary fragility was restored to normal. He noted with the administration of rutin the restoration to normal of capillary fragility which had been increased by thiocyanate therapy.

Donegan and Thomas,<sup>10</sup> treating with rutin 81 patients having increased capillary fragility, noted that there was some decrease in general capillary fragility in all. Two patients with occlusion of branches of the central retinal vein obtained no improvement with rutin therapy, while in a third patient there was marked improvement coincident with decrease in capillary fragility. Treatment with rutin was unsuccessful in 3 patients with high myopia and macular hemorrhages, in 3 patients with central choroiditis, and in 2 patients with disciform degeneration of the macula. Three patients with Eales' disease were treated with rutin. One of these showed marked improvement, 1 noted no change, and the third had a recurrence of hemorrhage into the vitreous while under treatment. They noted improvement in the retinal status

in "numerous instances" in their series of 20 patients with hypertension and various retinal complications. These authors also found complete disappearance of macular edema in 2 patients treated with rutin.

Soloff and Bello<sup>51</sup> conducted a study designed to recheck the results of capillary fragility tests in cases in which blood pressure was elevated and the presence of subclinical scurvy had been excluded. For this purpose, they administered 50 mg. of ascorbic acid, 50 mg. of niacinamide, 5 mg. of thiamine chloride and 3 mg. of riboflavin 3 times daily to each individual for 1 month before the tests were made. Twenty-five nonhypertensive and 50 hypertensive patients were studied. Among the 25 nonhypertensive patients, only 1, a diabetic patient, reacted positively to the Göthlin and Rumpel-Leede tests. Among the 50 patients with elevated blood pressure, only 2 gave positive reactions to the Göthlin test. One of these had diabetes. In 33 of these 50 cases (66%) results of the Rumpel-Leede test were positive. These authors stated that: "It is noteworthy that 3 of our 9 patients with retinal hemorrhages gave a negative Göthlin and Rumpel-Leede reaction . . . . There is obviously no correlation between a positive Rumpel-Leede reaction and the presence of retinal hemorrhages, as over 80% of our hypertensive patients with positive Rumpel-Leede reactions had no retinal hemorrhages." Soloff and Bello gave 20 mg. of rutin 3 or 4 times a day for a month to 10 of their patients who reacted positively to the Rumpel-Leede test. They noted no difference in the number of petechiae at the end of this time.

The source of the bleeding into the retina is not too clear in any of these reports on the vascular diseases. Presumptively, the hemorrhages were a part of hypertensive retinopathy and were not secondary to venous occlusion. A more definite idea as to the types of conditions treated is given in

the report of MacLean and Brambel.<sup>31</sup>

In a series of 21 patients having vascular retinopathies, MacLean and Brambel have employed simultaneous treatment with rutin and dicumarol, on the basis that there are two chief retinal vascular problems: (1) hemorrhage following capillary weakness and (2) vascular occlusion as the result of thrombosis, periphlebitis, atherosclerosis or constriction. For the first, rutin was used, and for the second, heparin or dicumarol, because of their anticoagulant action. There were 6 cases of partial occlusion of the central vein, 5 of degenerative retinopathy, 2 of central serous angiospastic retinopathy. Treatment with both dicumarol and rutin resulted in improvement in all cases. Two patients with Eales' disease were treated with rutin only, and 2 with occlusion of a retinal tributary vein with dicumarol only; all improved. The remainder had diabetes. The authors postulate that thrombotic tendencies are inhibited by the anticoagulant with resulting increased vascular efficiency followed by clearing of the involved retina.

Many reports have been made on the successful therapy with vitamin P of hemorrhagic disorders accompanied by increased capillary fragility. There are a few reports only of therapy of retinal hemorrhages by the use of vitamin P preparations other than rutin. Hanum<sup>22</sup> noted that under treatment with citrin the capillary resistance of 1 patient with retinitis proliferans increased but there was no change in the eyegrounds. Rudy and associates<sup>43</sup> gave hesperidin to 6 patients having diabetic retinopathy and increased capillary fragility with negative results. A similar patient was treated by Kirtley and Peck<sup>26</sup> with hesperidin methyl chalcone with apparently negative results. Pérez Allende<sup>39</sup> recommended vitamins C, K and P but presented no cases. Foxworthy's<sup>12</sup> results from use of hesperidin in diabetic retinopathy were disappointing, in that hesperidin tended to



decrease fragility but it had no effect on the retinal lesions. She subjected 85 nondiabetic patients and 69 diabetic patients without retinopathy and 44 with retinopathy to positive pressure tests and found an average time for the first appearance of petechiae to range from 4.9 minutes in the first group, to 2.36 minutes in the second group, to 1.5 minutes in the group with retinopathy. The number of petechiae which were present after 10 minutes were 14, 41 and 101 respectively. Saubermann<sup>44</sup> noted that with the intravenous use of 80 mg. of neohesperidin and of doses of vitamin C and calcium daily marked improvement occurred in vision in eyes in which there were old lesions of thrombotic type in the central vein, periphlebitis retinae, and Coats' disease, but no improvement in the vision when more recent lesions of the same type were present.

That diabetic retinopathy is an important part of the picture of diabetes mellitus, particularly in the cases of long duration, is shown by numerous studies. Wagener, Dry and Wilder<sup>54</sup> found retinopathy in 187 (17.7%) of 1,052 cases of diabetes, Waite and Beetham<sup>55</sup> in 18% of 2,002, Hanum<sup>22</sup> in 20.2% of 966 and Möllerström<sup>37</sup> on 5.1% of 2,166. Most authors have shown that the incidence is correlated more closely with the duration of the diabetes than it is with the age of the patient. Givner and Lodyjensky<sup>15</sup> reported on 128 diabetic patients who were less than 19 years of age; all 3 who had retinal changes were known to have had diabetes for 8 or more years. Wagener<sup>33</sup> noted an increasing incidence of retinopathy in cases of diabetes when his three series were compared. Retinopathy was present in 8.3% of the 1921 series of cases, in 17.7% of the 1934 series and in 30.6% of the 1945 series of 1,021 cases. He found retinopathy in 10.7% of patients who had had diabetes for less than one year, in 22% of those who had had it for from 1 to 10 years, in 65% of those who had had diabetes for from 11 to 15 years, in 67% of those

who had had it for more than 15 years and in 73% of those who had had the disease for 20 years or more. Dolger<sup>8</sup> followed for 25 years or more 200 patients who had diabetes and were less than 50 years of age at time of onset and found that none escaped retinal hemorrhages, albuminuria or hypertension or all three, in varying degree.

Treatment of diabetic retinopathy has been directed along many lines. Many authors are of the opinion that the fundamental basis for the onset of retinopathy lies in the poor control of the hyperglycemia. On the other hand, Mosenthal<sup>38</sup> concluded that the retinal hemorrhages were on the basis of hypoglycemic reactions and advised high enough levels of blood sugar to prevent such reactions. Schneider and co-workers<sup>46</sup> and Schwarz<sup>48</sup> stated that deficient tissue protein is the cause, and they recommended high protein diets. Many attempts have been made to reverse the process in the retina by the use of the various vitamin P substances. Throughout the literature it is remarkable that when a series of patients who have increased capillary fragility and permeability are treated, those patients who have diabetes mellitus seem to be the most refractory to restoration of the capillary status to normal.

The high incidence of increased fragility, as measured on the skin capillaries in cases of diabetes, seems significant, and points toward similar pathologic alterations in the retinal capillaries. However, the mechanism of production of diabetic retinopathy is not known. The vascular changes appear to affect the venous, rather than the arterial, side of the circulation, as on ophthalmoscopic examination enlarged and tortuous retinal venules are seen in many cases of diabetes. Perhaps the earliest observable change is the presence of micro-aneurysms in the capillaries of the retina as noted by Ballantyne,<sup>4</sup> who suggested that venous stasis was an early and essential factor in the development of diabetic retinopathy. It is possible then that capillary

fragility and permeability are increased and this increase accounts for the small hemorrhages and exudates so characteristic of diabetic retinopathy.

Most authors have noted a high incidence of capillary abnormality in patients who have diabetic retinopathy. Rodriguez and Root<sup>42</sup> found that 40% of 100 unselected diabetic patients had increased fragility, while 100% of 56 patients who had diabetic retinopathy had this derangement. Of the 40 unselected patients, 65% had retinopathy. Mallery<sup>36</sup> found increased fragility in 25% of 120 cases of diabetes and retinopathy in 25 (83%) of these. All of Hanum's 12 patients with retinitis proliferans had capillary abnormality. McFarland<sup>30</sup> examined 83 diabetic patients with retinopathy and found that 92% had increased capillary fragility. Beaser and associates<sup>9</sup> noted increased fragility in 24% of nondiabetic nonhypertensive patients with other diseases, in 53% of nondiabetic hypertensive patients, in 54% of diabetic nonhypertensive patients and in 100% of diabetic hypertensive patients. Wagener<sup>53</sup> quoted Foxworthy's studies on capillary fragility in cases of diabetes in which he later showed that the initial appearance of petechiae and the number of petechiae were considerably greater in diabetic patients with retinopathy than in those with normal retinas.

The treatment of diabetic retinopathy for the most part is attended by discouraging results. Dolger<sup>9</sup> stated, "Neither vitamin C nor vitamin P, rutin nor hesperidin influence retinal hemorrhages significantly and unequivocally. Evaluation of such therapy is difficult because of the spontaneous remissions and exacerbations displayed by these lesions. I have given up hope in the use of these substances as the results are not strikingly different from the control group." Givner<sup>14</sup> has made similar statements and noted that several patients have had retinal hemorrhages during the course of rutin therapy. Subconjunctival hemorrhages

also have been reported.<sup>59</sup> In a symposium on the subject of diabetic retinopathy, Palmer<sup>10</sup> stated, "We have used considerable rutin. I cannot be too enthusiastic about it." Joslin<sup>25</sup> stated that his group was not so pessimistic as Dr. Dolger, but were rather open-minded. Dr. White<sup>56</sup> said that with children who have used rutin the progress of the disease in the eyes has been less rapid. Wilder<sup>57</sup> stated that he and his co-workers have used it in a good many cases but the results could not be interpreted. Some patients who have had untreated retinitis in diabetes have improved spontaneously. He added further that patients who have improved during the administration of rutin may have deceived his group. At present they have an impression that in some of these cases the process has been arrested and its progress delayed by the use of rutin. Goedbloed reported a case of diabetes with retinopathy and increased capillary fragility in which the skin capillaries slowly returned to normal under treatment with 80 mg. of rutin daily but in which the retinal hemorrhages remained unchanged until 2 weeks after vitamin C was given in conjunction with the rutin, and then nearly all the retinal hemorrhages cleared. Levitt, Choltst and associates<sup>29</sup> treated 12 patients having diabetic retinopathy with 60 mg. of rutin daily for 2 months and 120 mg. daily for another month. These patients had been saturated with ascorbic acid as they had received 100 mg. 3 times daily for 1 month prior to therapy with rutin. They found it difficult to ascribe their results to rutin therapy. Only 4 patients showed improvement in skin capillary fragility. The retinal lesions in 5 eyes improved, but 2 of these patients showed no improvement in the fragility of the capillaries of the skin, and only 2 patients showed simultaneous improvement in retinal lesions and in fragility. One of their patients had a rapid progression of retinopathy to retinitis proliferans while under rutin therapy.

Donegan and Thomas<sup>10</sup> studied 45 patients having diabetes mellitus. Twenty-five of these had diabetic retinopathy. Despite a reduction in the general capillary fragility, there was little or no change in the retinopathy over a period of 3 to 12 months.

Rodriguez and Root<sup>42</sup> treated 20 patients with diabetic retinopathy for 8 months and found no observable change in the retinas of 13, absorption of hemorrhages in the eyes of 3, additional hemorrhages in 2, and arterial thrombosis in 2 while under therapy. Only 25% of their patients showed a return of the petechial index to normal or borderline figures. Shanno and associates<sup>50</sup> treated 79 patients who had retinal hemorrhage (34% had diabetes, 42% had hypertensive cardiovascular disease and the etiology of retinal hemorrhage in the remainder was not stated) and found that from 50 to 70% of patients recovered normal capillary integrity under treatment with rutin. They stated that these patients usually but not invariably failed to have further retinal hemorrhages. MacLean and Brambel<sup>31</sup> in their series of cases included 4 patients with diabetic retinopathy, none of whom had increased capillary fragility. However, 2 were placed on treatment with dicumarol only, while the other 2 received both dicumarol and rutin. All 4 patients had improved in visual acuity and absorption of hemorrhages.

It is fairly well established by numerous investigators that rutin has the property of restoring increased fragility of the skin capillaries to normal values in a large majority of patients so afflicted. In many patients this restoration is paralleled closely by a simultaneous improvement in the clinical condition. However, in the investigation of the effect of rutin therapy on the lesions of diabetic retinopathy and of other hemorrhages in the retina, additional factors complicate the picture. It is by no means certain that increased fragility and permeability of the skin capillaries are

accompanied by a corresponding dysfunction of the retinal capillaries. Much work that has been done certainly points toward that conclusion, but there are many discrepancies. Secondly, while some types of hemorrhage in the retina may be on the basis of vitamin P deficiency, there are many others which undoubtedly come from diverse other factors. Thirdly, the evaluation of clinical improvement in the retina is notoriously difficult, since superficial hemorrhages in the nerve-fiber layer of the retina may absorb spontaneously in a few days to a week, while more deeply placed hemorrhages may persist for a year or more. Moreover, hemorrhagic retinal lesions of all types are subject to frequent remissions.

It seems that the retinal complications of the diabetic are much more refractory to treatment with rutin than are some of the other types of hemorrhage in the retina. Certainly, the reports in the literature are much less enthusiastic with regard to lesions in cases of diabetes than to those in cases of hypertension and some of the purpuras. This lack of enthusiasm may be due in part to the slow course of diabetic retinopathy in the majority of cases, so that little change may be seen from month to month, while in most other types of retinopathy the hemorrhages are situated superficially so that absorption is more rapid.

Whether rutin therapy is actually of benefit in the treatment of hemorrhagic lesions in the retina cannot be answered dogmatically at this time with the material at hand. Certainly, its action on reversing increased capillary fragility in the skin and retina is not universally accepted. Furthermore, the relationships between hypertension, retinal hemorrhage and apoplexy in treated and untreated cases as reported by Griffith<sup>18</sup> are noteworthy, but they have not been confirmed fully by other investigators. With regard to the lesions in the retina associated with diabetes, it might be well to adopt the attitude of Rodriguez and Root.<sup>42</sup> They stated,

"Our studies show that capillary resistance is definitely low in practically all persons with diabetic retinitis. We suggest the desirability of further trial of this substance [rutin]. More important, however, is the possibility that through further investigation of the

pharmacology of rutin, we may ascertain the indications of its early use, in the hope of preventing the capillary damage related to the retinal and perhaps other degenerative complications in subjects with diabetes of long duration."

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# BOOK REVIEWS AND NOTICES

GRAY'S ANATOMY OF THE HUMAN BODY. Revised and Edited by CHARLES MAYO GOSS, M. D., Prof. of Anatomy, Louisiana State University. 25th ed. Pp. 1478; 1263 ill., mostly in color. Phila.: Lea & Febiger, 1948. Price, \$14.00.

THE continued prosperity of "Gray" through 25 editions extending over 90 years is surely a record for a medical textbook. It speaks well both for the intrinsic value of the book and for the skill of successive editors in keeping it abreast of continuing advances. The return to a single editor in this edition is accompanied by a number of changes in text and illustrations, especially in the section on muscles and fasciae, where the editor could use the results of his own unpublished research. The chapter references have been considerably expanded, so as both to include a recent bibliography for each and to "introduce the names of as many contemporary anatomists as possible." (For earlier reviews see the November, 1942; the March, 1937; and the November, 1930, numbers of this Journal.) E. K.

THE CARE AND MANAGEMENT OF LABORATORY ANIMALS. Edited by ALASTAIR N. WORDEN, M.A. (Cantab.), B.Sc. (Lond.), Milford Prof. and Director of Research in Animal Health, Univ. College of Wales. Pp. 368; 70 figs. Balt.: Williams & Wilkins, 1947. Price, \$8.50.

THIS book opens with a chapter on the laws which govern the use of experimental animals, with detailed discussions of construction, equipment and management, and of pests and their control in the animal laboratory. Then follow 19 chapters on as many types of laboratory animal, each containing sections on stock, breeding cages, bedding, food requirements, handling, anesthesia and euthanasia, and diseases and their control, and each ending with a well selected list of references. The common types such as guinea pigs, rabbits, rats and mice and their wild relatives are given adequate space, but in addition the wood mouse, deer mouse, cotton rat, the voles, hamsters, ferrets, hedgehogs, pigeons, canaries, amphibians and fish are considered. An appendix on statistical analysis and indices of subjects and authors complete the book. Although the book has been prepared chiefly by British experts for use in

Great Britain, it will be highly valuable to all who are concerned with laboratory animals. H. R.

MATHEMATICAL ANALYSIS OF BINOCULAR VISION. By RUDOLF K. LUNEBURG, Dartmouth Eye Institute. Pp. 104; 82 figs. Princeton, N. J.: Princeton University Press, 1948. Price, \$2.50.

THIS book presents a mathematical theory of visual perception. The author believes that the qualities in a particular visual sensation can be coordinated to the points of a three-dimensional geometrical manifold. The result is a geometrical map of visual sensation. An example of this is the ordinary Euclidean map of binocular vision which can be made by the intersection of two projection lines drawn from 2 fixed points in space. The base points are the centers of rotation of the eyes, and the projection lines the optical axes.

The author states that we cannot be sure that this map truly represents the sensed qualities of form and localization of objects. This would be the case if the apparent distance of any 2 sensed points were always proportional to the geometrical distance of the associated points of the Euclidean map. But this is not true. The sensed size of astronomical objects is in no way proportional to astronomical dimensions. The problem is, therefore, to find a coordination of sensed points of a visual sensation to the points of a geometrical manifold such that the apparent distance of any 2 sensed points is always proportional to the geometrical distance of the correlated points. Such a coordination is called a psychometric coordination.

THIS does not answer the question whether visual space is a Euclidean or non-Euclidean manifold. Environment may be explored by making physical measurements, and the space so mapped out, called the physical space, which must be distinguished carefully from the visual space. The visual and physical space may be correlated but the relation is not necessarily a one-to-one correspondence.

THE author concludes that the geometry of visual space is the hyperbolic geometry of Lobachevski. Differential formula establishes a relation between the visual and the physical space. This supports the general hypothesis that for an individual observer the apparent size of a lined element is uniquely determined by its physical coordinates. Our scale of size

seems to contract certain localizations of the lined element. Such a contraction can only be understood if there is a physiologic basis for it, either in the dioptic system of the eyes, on the retina, in the transmission to the brain, or in the cortex itself.

This monograph does not attempt to make any hypothesis about the question, and is intended only for those who are thoroughly familiar with mathematical analyses. F. A.

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**WIDENING HORIZONS IN MEDICAL EDUCATION.** Edited by JEAN A. CURREN, M.D., President and Dean, Long Island College of Medicine, and ELEANOR COCKERILL, Professor, School of Social Work, University of Pittsburgh. Pp. 228. New York: Commonwealth Fund, 1948. Price, \$2.75.

THIS is a report of the Joint Committee of the Association of American Medical Colleges and the American Association of Medical Social Workers. It suggests that the medical student should be made to realize that "Man is a biological and social being, and medicine is a natural and social science. . . . The student must learn to recognize the social and environmental factors in every case. He must develop certain attitudes that will help him to establish effective and wholesome relationships with the patient and his family, and with his own colleagues. . . . This study may be regarded as an initial probing of a subject that has broad implications and many facets. It is clear that medical social teaching is undergoing rapid change and growth." Numerous detailed case reports are included in the book which illustrate the points stressed by the authors. They make recommendations for improvement in the teaching of this field.

This book will be of special value to all teachers in the fields of medicine and social work.

R. B.

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**A SYMPOSIUM ON THE USE OF ISOTOPES IN BIOLOGY AND MEDICINE.** Pp. 445; 58 ills., photographs of speakers. Madison: University of Wisconsin Press, 1948. Price, \$5.00.

IN September of 1947, at a meeting sponsored by the Wisconsin Alumni Research Foundation, a group of prominent scientists discussed the advances that have been made in the application of isotopic methods to research in biology and medicine. The papers presented by 19 of these authorities are published in this book; together they comprise an inclusive review of the subject.

Eight of the articles are concerned with historical background and with a discussion of the preparation, separation, and assay of isotopes

and their incorporation into compounds. Of particular interest to medical men will be the sections on the use of tracers in the study of intermediary metabolism and on the possible medical applications of these findings. In addition, there are several essays dealing with precautions to be taken in handling radioactive materials and with the subject of international control of atomic energy.

The fact that the authors are distinguished leaders in their fields strongly recommends this book to those who are interested in a general survey of the subject. It is to be regretted that the panel discussions, one of the most stimulating aspects of the Madison meeting, were not also published. M. C.

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**READING AND VISUAL FATIGUE.** By LEONARD CARMICHAEL, Ph.D., President, Tufts College, and WALTER F. DEARBORN, M.D., Ph.D., Director, Psycho-educational Clinic, Harvard. Pp. 483; 103 figs. Boston: Houghton Mifflin, 1947. Price, \$5.00.

THIS book is the outcome of a series of studies made by the authors in the laboratories of Tufts College and in the Harvard Clinic. The first chapter defines visual fatigue. Considerable space is given to a general resumé of the anatomy and physiology of the ocular apparatus. Chapter 2 deals with the mechanics of reading as a visual task. Chapters 4, 5 and 6, review the evidence demonstrating the nature of the effect certain environmental variables have upon reading behavior.

A review is then given of the various means of recording eye movements during reading, followed by the authors' own experiments. They were unable to show any fatigue on the part of a normal subject reading continuously for six hours. Similarly, they conclude that microfilm reading can be carried on for six hours without unduly fatiguing the normal subject.

The book should be valuable for those interested in the psychophysiology of reading.

F. A.

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**THE ACUTE BACTERIAL DISEASES, THEIR DIAGNOSIS AND TREATMENT.** By HARRY F. DOWLING, M.D., F.A.C.P., Clinical Prof. of Medicine, George Washington Univ. With the collaboration of LEWIS K. SWEET, M.D., and HAROLD L. HIRSCH, M.D. Pp. 465; 55 figs. Phila.: W. B. Saunders, 1948. Price, \$6.50.

THIS book will be found valuable by both student and practitioner. In Part 1, the first of the book's 4 sections, there are included tables of infectious diseases characterized by

## BOOK REVIEWS AND NOTICES

particular clinical manifestations such as fever, eruption, pharyngitis, and so on. Also in Part I, there are excellent discussions of serum therapy, sulfonamide therapy, penicillin and streptomycin therapy, in which are included indications, dosages, routes of administration, toxic manifestations and the like.

Descriptions of the diseases themselves are grouped according to the type of organism responsible—Part 2 deals with the diseases caused by cocci, Part 3 those caused by bacteria, and Part 4 those in which exotoxins are a major factor. Generally, discussions of individual diseases are concerned primarily with clinical and laboratory diagnosis and with treatment, both of which are presented very clearly and with specific directions. Etiology, pathology and pathogenesis are mentioned only briefly. Although the descriptions are not especially profound, the subject matter is quite complete and clearly expounded. A group of miscellaneous diseases, including colon bacillus infections, pseudomonas infections, glanders and botulism, is treated briefly.

There are 55 excellent color photographs and clinical records of patients, and 52 instructive tables. An adequate bibliography is included. The author has drawn heavily from his own experience and from a comprehensive examination of the literature. The book has much to recommend it to the clinician. S.E.

**PSYCHOSOCIAL MEDICINE. A STUDY OF THE SICK SOCIETY.** By JAMES L. HALLIDAY, M.D., Department of Public Health, Scotland. Pp. 278. New York: W. W. Norton, 1948. Price, \$3.50.

This important book discusses the sickness of society. It looks beyond the individual patients to whom physicians devote most of their attention to the health of large groups (coal miners) or nations about which physicians must come to think if they wish to have anything to say about the world they live in. A clear diagram gives much of the writer's argument: it shows the general death rate, the tuberculosis and typhoid rates and others on a down curve from 1900 to 1939; but crossing this curve in an up-sweep are suicides, peptic ulcer, hypertensive disorders and the infertility rate. The author has comments on the biological and mechanistic viewpoints in etiology in an important first chapter, and statistics of psychosomatic medicine in Part 2. His description of the training of infants in 1890 and in 1940 should not be missed. Accounts of the epidemiology of psychosocial disorders and of the growing anxiety in the modern world are other parts of a valuable and original book. E. B.

**TEXTBOOK OF ENDOCRINOLOGY.** By HANS SELYE, M.D., Ph.D., D.Sc., F.R.S., Institut de Médecine et de Chirurgie expérimentale, Université de Montréal. Pp. 916; 200 ills. Montreal: Acta Endocrinologica, Université de Montréal, 1948. Price, \$12.80.

This is an authoritative and profusely illustrated textbook dealing with the clinical problems of endocrinology as well as the laboratory investigations necessary for an understanding of the fundamental basis of this large field. At the same time it is an atlas of endocrinology with the equivalent of 200 pages of half-tone engravings, drawings and other illustrative material.

The book is designed primarily for the physician and specialist in endocrinology. It attempts to cover both the clinical and theoretical backgrounds of endocrinology. The pertinent anatomy, embryology and pathology receive much attention as well as a comprehensive discussion of the biological chemistry involved. The chemistry is simply and clearly presented. Where there are questions of interpretation or differences of opinion the author presents the evidence and attempts to evaluate it.

This is a well-rounded treatise in endocrinology which could well be in the library of every physician and endocrinologist. The printers have done a superb job. S. G.

**MANUAL FOR LABORATORY WORK IN MAMMALIAN PHYSIOLOGY.** By FRED E. D'AMOUR and FRANK R. BLOOD. 50 Experiments, illustrated. Chicago: Univ. of Chicago Press, 1948. Price, \$2.75.

This manual of techniques and procedures on rat physiology gives many helpful hints. The authors prefer to record results with ink-writing instruments instead of smoked drums. Each experimental procedure and operation is clearly illustrated by photographs. These are the most helpful and useful part of the book. Sample calculations can be concluded in general, each experiment can be concluded within 3 hours, though experiments on the endocrine system and on anaphylactic shock often require several weeks. The small size of the rat makes manual dexterity and sound anatomical knowledge essential. In addition, numerous delicate and specialized instruments will be required for the many different methods; and some, such as the exposure of the splanchnic nerves by the dorsal approach, seem too difficult for the beginner. R. E.

**OCCUPATIONAL MEDICINE AND INDUSTRIAL HYGIENE.** By RUTHERFORD T. JOHNSTONE, M.D., Consultant in Industrial Health and



Lecturer, Univ. of California. Pp. 604; 117 ills., 7 in color. St. Louis: C. V. Mosby, 1948. Price, \$10.00.

THIS textbook of occupational disease is written with broad understanding of the problems of industrial hazards. Although comprehensive, the book is not pedantic; the practical objectives of diagnosis, protection, and treatment are always foremost. The first few chapters consist of general remarks concerning functions of the industrial physician. The remainder of the book is devoted to a systematic consideration of the various substances encountered in industry. In each instance there is a brief orientation as to the chemistry and uses of the material; then symptomatology, pathology, diagnosis, and treatment of the respective disease are discussed. Illustrative case reports and accounts of animal experimentation are included. Numerous photographs of pathological and clinical material accompany the text; a useful appendix of chemicals in common trade-name products is provided.

A. R.

#### DISEASES OF THE JOINTS AND RHEUMATISM.

By KENNETH STONE, D.M. (Oxon.). M.R., C.P. Pp. 362; 58 ills. New York: Grune & Stratton, 1947. Price, \$6.50.

THE author knows the field of rheumatism well. This book is one of the most concise works on the rheumatic diseases, yet presents arthritis and the related diseases in an excellent descriptive manner. Throughout are good detailed descriptions of physical findings and the chapter on How to Examine Joints is particularly commendable. It is an excellent book for students. The terminology, that of the British, at times may be a little confusing. Discussion of the treatment of Rheumatoid Arthritis is somewhat sketchy and incomplete, but is certainly not as confusing as the discussions in some larger books on this subject. The section of the book on Muscular Rheumatism contains much hypothetical material which is open to considerable argument, but which certainly is as good reasoning as that conceived with most theories on the origin of fibrositis.

This book should be on the required list for any graduate student studying the diseases of the joints.

J. H.

BRIEF PSYCHOTHERAPY. By DR. BERTRAND S. FROHMAN, M.D., with the collaboration of EVELYN P. FROHMAN. Foreword by WALTER C. ALVAREZ, M.D. Pp. 265. Phila.: Lea & Febiger, 1948. Price, \$4.00.

THIS book can be accepted as a practical handbook on the neuroses for the general practitioner. The psychiatrist will want to know that the author favors the ideas of Stekel.

Classification of the neuroses occupies 20 pages and a description of neurotic mechanisms takes 20 more. Etiology is given 46 pages in simple terms—"The Revolt Against The Home, School, and Church", with 100 illustrative cases in single paragraphs. Therapy in general is Active Analysis with the warning that "frank neurotic states are best left untouched by inexperienced hands". Included are 14 interesting pages on the uses of semantics in treatment.

A glossary for patients is an unusual feature.

E. B.

THE SPLEEN AND HYPERSPLENISM. By WILLIAM DAMESHEK, M.D., and SOLOMON ESTREN, M.D. From the Pratt Diagnostic Hospital and Tufts Medical School, Boston. Pp. 50; illustrated. New York: Grune & Stratton, 1947. Price, \$4.75.

DAMESHEK and Estren have again made available as once before, in attractive, loose-leaf, monograph form, the panels they exhibited at the last annual meeting of the American Medical Association, June, 1947. In outline form are presented the demonstrated anatomy, histology and physiology of that enigmatic organ, the spleen, and the suspected hyposplenic and hypersplenic functional pathology as it occurs in human disease syndromes.

An "exaggerated splenic hormonal" inhibition of bone marrow maturation and delivery of cells is hypothesized, with prompt correction reported following successful splenectomy in selected cases. Peripheral blood and sternal marrow studies are emphasized in the differential diagnosis. The adrenalin test for the demonstration of splenic cellular hypersequestration and the histopathologic evidence of splenic reticulo endothelial cell hyperphagocytosis in many of these syndromes are minimized. This brochure is a very clear, somewhat dogmatic (because of its form and purpose), treatise on the indications and contraindications for human splenectomy in both primary and secondary hypersplenic states.

C. D.

#### DIABETES MELLITUS IN GENERAL PRACTICE.

By ARTHUR R. COLWELL, M.D., Assoc. Prof. of Medicine, Northwestern Univ. Pp. 350; 24 figs. Chicago: The Year Book Publishers, 1947. Price, \$5.25.



THIS monograph contains the conventional chapters on diagnosis and treatment of diabetes and its complications. Dr. Colwell's skill as a teacher is revealed in the excellent organization of the subject and in his clear summary of the modern understanding of this disease. In the aspects of diabetes which are controversial he avoids extremes and maintains the practical clarity which the physician who is not a specialist in diabetes requires. He does not mention the use of potassium and phosphate in the treatment of acidosis, though these adjuncts now appear to merit wider use. The figures are well selected and some of the elementary tables showing the responses to treatment deserve careful study. The author's purpose that "the book's contents include the best and soundest of available insight and methods of treatment, presented from a practical standpoint and organized in such a manner that the reader who lacks experience with diabetes should have little difficulty in orientation", has been excellently fulfilled.

F. L.

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HALLMARKS OF MANKIND. By FREDERIC WOOD JONES, D.Sc., M.B., B.S., F.R.S., F.R.C.S., and SIR WILLIAM COLLINS, Prof. of Human and Comparative Anatomy, Roy. Coll. of Surgeons. Pp. 86; 23 illus. Balt.: Williams and Wilkins, 1948. Price, \$2.50.

THIS delightful little book contains the subject matter of a Linacre Lecture and an Arris and Gale Lecture delivered in 1947. Its main thesis is that Man, considered solely from the point of view of structure, is an extremely primitive type and, though more primitive in basal structure than the living monkeys and apes, Man has his own remarkable structural specifications that distinguish him from all other Mammals and appear to be his very ancient hallmarks. The authors postulate that the emergence of the human type from a very primitive Primate form took place sufficiently far back to account for the profound differentiation that has occurred. They believe that if the Primate forms immediately ancestral to the human stock are ever to be revealed, they will be utterly unlike the slouching, hairy, "ape men" of which some have dreamed and will be found in geologic strata antedating the heyday of the great apes.

The book should be of special interest to those who assume that the use of monkeys of any sort for experimental work may be justified on the basis of a close relationship to Man.

W. F.

THE THYROID AND ITS DISEASES. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University. 2d ed. Pp. 571; 63 illus. Philadelphia: J. B. Lippincott, 1948. Price, \$12.00.

THE ADVENT of the 2d edition of this notable book should receive a warm welcome from all who have enjoyed the 1st, which appeared in 1937. This volume clearly reflects the tremendous advances in our knowledge of the normal and abnormal physiology of the thyroid and the treatment of its diseases during the intervening 11 years, to the development of which the author and his associates have been important contributors. There are 21 chapters dealing with the embryology, anatomy, physiology, endocrine relationships, pathology and clinical disorders of the thyroid. The chapter on Surgery of the Thyroid was prepared by Dr. Oliver Cope; those on the Pathology and Tumors of the Thyroid were written by Dr. Rulon W. Rawson.

The style is informal, sometimes almost conversational, and makes for easy reading. Throughout, the book is strongly flavored by the personality of the author; this is particularly apparent in the delightful last chapter entitled "Fact and Fancy in Matters Thyroid". There can be little doubt that this is the foremost work available in its field today, and it deserves a place on the shelf of all who are interested in thyroid disease.

E. R.

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CLINICAL LABORATORY METHODS AND DIAGNOSIS. By R. B. H. GRADWOHL, M.D., D. Sc., F.R.S.T.M.&H. (London), Director of Gradwohl Laboratories, St. Louis, Mo., and DR. PEDRO KOURI, Director of Tropical Medicine, Havana, Cuba. 4th ed. 3 volumes. Pp. 3291; 1111 illus., 58 in color. St. Louis: C. V. Mosby, 1948. Price, \$40.00.

THE new edition of this well known treatise has been greatly expanded with 55% more text matter and 51% more illustrations. The section on parasitology and tropical medicine has been increased from 394 to 820 pages and now constitutes a separate volume. This excellent section describes over 175 parasites, protozoan and metazoan, important in human medicine, with 427 illustrations. The expanded sections on hematology and on blood transfusion are admirable. Bacteriologic applications in clinical diagnosis have been extended by 151 pages; 49 pages have been added on toxicologic technique; and a new chapter on electrocardiography is included.

Autopsy technique is not fully described in detail, but since this procedure is performed by the pathologist himself, this limitation is perhaps not important. The adaptation of photoelectric colorimetry to chemical procedures is inadequately presented and a number of other accepted improvements in chemical methods receive no mention. Quantitative methods are described throughout without any reference to the importance of evaluating quantitatively the error of measurement.

Such deficiencies, however, are far outbalanced by the great mass of well arranged and admirably illustrated information covering the field of clinical laboratory technology and interpretation.

Indexing, which occupies 175 pages, appears adequate. J. A.

### NEW BOOKS

*Technique of Treatment for the Cerebral Palsy Child.* By PAULA F. EGEL, Children's Hospital, Buffalo. Pp. 203; 49 ills. St. Louis: C. V. Mosby, 1948. Price, \$3.50.

*The Story of The Johns Hopkins.* By BERTRAM M. BERNHEIM, M.D. Pp. 235. Illustrated. New York: McGraw-Hill, 1948. Price, \$3.50.

THE author, an early graduate of the Hopkins Medical School (1905) and long connected with it, has told in colloquial style "a human interest story with historical connotations." Sympathetic in the main, but with occasional barbed criticisms the story will be found to include enough details to provide a lively and satisfying picture of this great school and its famous men. E. K.

*Medical Clinics of North America.* Boston number. "Specific Methods of Treatment." Pp. 1159-1482. Phila: W. B. Saunders, September, 1948. Price, \$15.00 a year.

AMONG the subjects considered are: Penicillin in pulmonary infections, antispasmodics and spasmodics in gastrointestinal disorders, treatment of various types of anemias, management of rheumatoid arthritis, medical management of essential hypertension, treatment of migraine, diagnosis and treatment of poliomyelitis, and treatment of rickettsial diseases. Practical aspects of management and recent developments are emphasized. There is a detailed discussion of the problem of infertility, and of the medical management of urinary calculi based upon the chemical composition of the stone. The

description of the practical aspects of the care of patients with spinal cord injuries by Monroe, and of nutrition in protracted disease by Stare and co-workers are particularly interesting and useful, as is a discussion of brief psychotherapy in medical practice, and of repair solutions in acidosis and alkalosis. R. J., Jr.

*A-B-C's of Sulfonamide and Antibiotic Therapy.* By PERRIN H. LONG, M.D., F.R.C.P., Prof. of Preventive Medicine, Johns Hopkins Univ. Pp. 231. Phila.: W. B. Saunders, 1948. Price, \$3.50.

WRITTEN for the practitioner, this book presents the author's clinical experience with sulfonamide, penicillin and streptomycin. Dosage schedules, pharmacology, and the toxic manifestations of each drug are presented for the chemotherapy of over a hundred infectious processes. There is no bibliography. G. R.

*Neurosurgical Pathology.* By I. MARK SCHEINKER, M.D., Univ. of Cincinnati College of Medicine. Pp. 370; 238 ills. Springfield, Ill.: Charles C Thomas, 1948. Price, \$8.75.

*Viral and Rickettsial Infections of Man.* Edited by THOMAS M. RIVERS, M. D., Director of the Hospital, The Rockefeller Institute. Pp. 587; 77 ills., 6 in color. Phila.: J. B. Lippincott, 1948. Price, \$5.00.

*ANA Public Relations Workshop.* By EDWARD L. BERNAYS. Pp. 32; 39 ills. New York: American Nurses' Association, 1948. Price, \$2.50.

A MANUAL of practical public relations techniques for American nurses.

*Medical Research in France During the War (1939-1945).* 30 articles presented by JEAN HAMBURGER, Professeur agrégé à la Faculté de Médecine. Pp. 306. Illustrated. Paris: Éditions Médicales Flammarion, 1948. No price given.

" . . . some results of the scientific work accomplished by French physicians and biologists during the German occupation."

*Therapy Through Interview.* By STANLEY G. LAW, M.D., Minnesota Psychiatric Institute. Pp. 313. New York: McGraw-Hill, 1948. Price, \$4.50.

After years of general practice, the author having become especially interested in our more common psychoneuroses, developed a unique method of studying his patients. The "interview techniques" employed are chiefly for the general practitioner, who is told in forthright simple language, "how to listen and to talk to patients," through case presentations con-

cerning wholly imaginary subjects. Psychiatrists may consider this dialogue method an over-simplification; however, professional associates are said to view the author's work with favor. N. Y.

*Strabismus. A Clinical Handbook.* By GEORGE J. EPSTEIN, M.D., Beth Israel Hospital, New York. Pp. 224; 123 ills. Phila.: Blakiston, 1948. Price, \$5.00.

THIS is the third book to appear within the year on abnormalities of the ocular muscles, which attests to the interest in this subject. This volume summarizes the anatomy and physiology of the extra-ocular muscles and the modern conceptions of squint. While the major portions of its contents are of interest to ophthalmologists, the author's lucid style will afford the general practitioner a good working knowledge of the modern treatment of squint. It can be recommended to all interested in the subject. F. A.

*Father Land.* By BERTRAM SCHAFFNER, M.D. Pp. 203. New York: Columbia University Press, 1948. Price, \$3.25.

THE AUTHOR, a neuropsychiatrist, served with the Information Control Screening Division of the American Military Government in Germany, and in this capacity performed psychiatric examinations and conducted psychologic tests, studies and opinion surveys among the German people. *Father Land*, a result of this experience, traces German authoritarianism to its origin in the family circle, and suggests complete re-education beginning at the family level as an important step in producing a Democratic Germany. R. E.

*Your Baby.* By GLADYS DENNY SHULTZ, and LEE FORNEST HILL, M.D. Pp. 278. Illustrated. Garden City, N. Y.: Doubleday, 1948. Price, \$3.50.

"THROUGHOUT these pages we have thought of the father quite as much as of the mother. . . . We should like to emphasize that this book is intended only as a supplement to regular medical care. Spaces are left throughout the book for inserting your own doctor's advice."

#### NEW EDITIONS

*Medical Writing.* By MORRIS FISHER, M.D. 2d. ed. Pp. 292; 36 ills. Phila.: Blakiston, 1948. Price, \$4.00.

*Bailey's Textbook of Histology.* Revised by PHILIP E. SMITH, Ph.D., and WILFRED M. COPENHAVER, Ph.D. 12th ed. Pp. 781; 455

ills., many in color. Balt.: Williams & Wilkins, 1948. Price, \$7.00.

THE REVISERS continue to aim at a text "primarily for the use of first year students in medicine and dentistry", including physiological significances and more bridges of the gap between gross and microscopic anatomy.

*A Textbook of Histology.* By ALEXANDER A. MAXIMOW, late Prof. of Anatomy, Univ. of Chicago, and WILLIAM BLOOM, Prof. of Anatomy. 5th ed. Pp. 700; 562 ills., 32 in color. Phila.: W. B. Saunders, 1948. Price, \$8.50.

*A Method of Anatomy.* By J. C. BOILEAU GRANT, M.C., M.B., Ch.B., F.R.C.S. (Edin.) Prof. of Anatomy, Univ. of Toronto. 4th ed. Pp. 852; 799 ills. Balt.: Williams & Wilkins, 1948. Price, \$7.00.

*A Method of Anatomy* has proved its value through 3 previous editions, the first one appearing in 1937. This edition has been improved in a number of ways, most notably by the addition of 68 new illustrations. Professor Grant's book differs from the more commonly known textbooks of anatomy by treating the subject regionally rather than systemically. When used in conjunction with his *Atlas of Anatomy* it provides the first year medical student with exceptionally good instructions for his work. There are many descriptions throughout the book that will be of interest to anyone seeking to recall his knowledge of the structure of the human body. W. W.

*Clinical Roentgenology of the Digestive Tract.* By MAURICE FELDMAN, M.D., Asst. Prof. of Gastroenterology, Univ. of Maryland. 3d ed. Pp. 901; 641 ills. Balt.: Williams & Wilkins, 1948. Price, \$8.00.

THIS book attempts to cover all those aspects of gastrointestinal disease that are of interest to the roentgenologist. It includes, therefore, data on the incidence, the etiology and the symptomatology as well as the roentgen diagnosis of digestive tract lesions. Only their treatment is omitted. Consequently, though a large volume, it presents the individual subjects merely in outline. At the same time the illustrations are excellent and many references are given. The student, whether interested primarily in gastroenterology or radiology, will profit by reading it and by having it available for reference. T. M.

*Cancer Manual.* Edited by A. W. ERSKINE, S. F. SINGER, D. F. WARD. Cancer Committee of the Iowa State Medical

Society. 2d ed. Pp. 160. Iowa City, Iowa: Athens Press, 1948. Price, \$1.00.

This work is a concise manual, presenting the essential clinical facts about cancer, and brought thoroughly up to date. It is devoted primarily to symptomatology and methods of diagnosis of the more common malignant growths. Emphasis throughout is on early diagnosis.

The treatment of some subjects is confusing and at times only one aspect of highly controversial points is given mention. The section on cancer of the breast suffers from both these faults. These criticisms should not detract greatly from the value of a compendium designed primarily to keep the general practitioner alert to the diagnosis of cancer. However, it does seem that the importance of biopsy might be more generally stressed—indeed, it is stated to be rarely necessary in cancer of the rectum.

R. H.

*The Therapy of the Neuroses and Psychoses.* By SAMUEL HENRY KRAINES, M.D., Asst. Clinical Prof. in Psychiatry, Univ. of Illinois, College of Medicine. 3d ed. Pp. 642. Phila.: Lea & Febiger, 1948. Price, \$6.50.

THE 3d edition, like the preceding editions of this book, approaches Psychiatry mainly from a psychobiological rather than a psychoanalytic viewpoint. It contains new sections on psychiatric geriatrics, pre-frontal lobotomy, group psychotherapy, treatment of epilepsy, a revised classification of psychiatric disorders, and statistical tables on mental disease.

W. P.

*Manual of Urology.* By R. M. LeCOMTE, M.D., F.A.C.S., Georgetown University. 4th ed. Pp. 311; 57 ills. Balt.: Williams & Wilkins, 1948. Price, \$4.00.

"No attempt has been made to alter the original purpose of the book—to present briefly and simply the underlying principles in urology without complicating discussions, case histories and numerous references."

*Handbook of Orthopaedic Surgery.* By ALFRED RIVES SHANDS, JR., M.D., with RICHARD BEVERLY RANEY, M.D. 3d ed. Pp. 574; 159 ills. St. Louis: C. V. Mosby, 1948. Price, \$6.00.

This new edition continues the high excellence of previous editions. The author has carefully revised it, adding new and worthwhile developments in orthopaedic surgery. The introduction of a few Roentgen ray photographs replacing some of the man pen and ink sketches in previous editions is thought to add clarity to the text and make the book more valuable to the student. The author is to be

congratulated on bringing this book up to date as a teaching manual and a reference book for the advanced student.

P. C.

*Zinsser's Textbook of Bacteriology.* Revised by DAVID T. SMITH, M.D., DONALD S. MARTIN, M.D., M.P.H., NORMAN F. CONANT, Ph.D., JOSEPH W. BEARD, M.D., GRANT TAYLOR, M.D., HENRY I. KOHN, Ph.D., M.D., and MARY A. POSTON, M.A., Duke University School of Medicine. 9th ed. Pp. 992; 251 ills. New York: Appleton-Century-Crofts, 1948. Price, \$10.00.

THE basic approach is from the combined viewpoint of the clinician, researcher, and teacher. The arrangement of the chapters remains about as in the 8th edition. However, the text has been brought up to date as well as a section on antibiotics and a chapter on pleuropneumonia-like organisms added. It contains no material on parasitology.

H. M.

*Microbiology and Pathology.* By CHARLES F. CARTER, M.D., Parkland Hospital School of Nursing, Dallas, Texas. 4th ed. Pp. 845; 216 ills.; 25 color plates. St. Louis: C. V. Mosby, 1948. Price, \$5.00.

ALL CHAPTERS have been revised, some very extensively, and new material added. Sulfonamide and antibiotic therapies are discussed. Chapters on Approved Methods of Immunization, Hospital Pathologist and His Work, and Defects of Body Development have been included.

H. M.

*Sterility and Impaired Fertility.* By CEDRIC LANE-ROBERTS, C.V.O., M.S., ALBERT SHARMAN, M.D., Ph.D., KENNETH WALKER, M.A., M.B., B. P. WEISNER, D.Sc., Ph.D., and MARY BARTON, M.B., B.S. 2d. ed. Pp. 400; 96 ills. New York and London: Paul B. Hoeber, 1948. Price, \$6.50.

*Fractures and Dislocations.* By EDWIN O. GECKELER, M.D. 4th ed. Pp. 371; 344 ills. Balt.: Williams & Wilkins, 1948. Price, \$5.00.

THIS compact small text has grown larger and more complete in each successive edition. The present volume is to be highly recommended, not as an exhaustive book on the large subject of fractures and dislocations, but as the outcome of a careful personal selection of methods of treatment that will assure good functional results. Both the student and general practitioner interested in bone and joint disabilities will find this one of the best small books published.

P. C.

*Diseases of the Eye.* By SIR JOHN HERBERT PARSONS, Consulting Ophthalmic Surgeon, University College Hospital, etc., and SIR STEWART DUKE-ELDER, Surgeon Oculist to the King, Consulting Ophthalmic Surgeon to the Army and Royal Air Force, Director of Research, The Ophthalmic Institute, University of London, etc. 11th ed. Pp. 732; 368 figs., 21 plates. New York: Macmillan, 1948. Price, \$7.00.

THIS is an excellently prepared short text which now includes all the recent advances

in ophthalmology. The section on glaucoma is particularly good, as it includes the modern conception of shallow angle and deep angle type which is adopted in very few standard texts.

While the book contains far too much specialized knowledge for the medical student, it should be a useful reference book for the general practitioner and will certainly be of value to the trained ophthalmologist, as it represents the opinions of two world authorities. F. A.

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### CORRECTION

In the abstract in the November issue (216, 598, 1948) of *Construction of Normal Standards for Cardiac Output in Man* by J. M. Tanner, the root signs were omitted from the formula, which should be:

$$SV \text{ (ml)} = 100 \sqrt{2 \text{ area } I + \text{area } J} \sqrt{c}$$

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MARCH 1949

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## ORIGINAL ARTICLES

### STUDIES OF THE HUMAN COLON:

#### I. VARIATIONS IN CONCENTRATION OF LYSOZYME WITH LIFE SITUATION AND EMOTIONAL STATE<sup>\*†</sup>

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LYSOZYME, a bacteriolytic and mucolytic enzyme, was first described by Fleming in 1922<sup>2</sup>, when he was studying the anti-bacterial properties of tears. Since then the enzyme has been shown to be present not only in human tears<sup>2,7</sup> but also in nasal mucus<sup>12</sup>, gastric juice, the secretions of the large and small intestines<sup>3,4,7</sup> and human milk<sup>1</sup>. All pathologic transudates and exudates contain large amounts<sup>13</sup>. The richest source of this lytic enzyme is egg white of hen's eggs. Further studies<sup>5,9,11</sup> on this substance have shown it to be a basic protein or polypeptide containing about 16% nitrogen and 2 or 3% sulphur. It is of small

molecular size, having a diameter of less than 30 millimicrons. It is soluble and heat stable in acid solution, but insoluble and heat labile in alkaline solutions.

Recent studies on the substrate of this enzyme by Karl Meyer and his associates<sup>6,7</sup> have shown that the enzyme depolymerizes certain high molecular weight amino carbohydrates which they have isolated from susceptible organisms (*Micrococcus Lyso-deitkicus* or *Sarcina Lutea*). However, the search for the substrate of lysozyme in various organs of the body has thus far been fruitless.

Lysozyme concentrations can be

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† Aided by grants from the Lester N. Hofheimer Foundation.

measured by determining the rate of clearing of opaque suspensions of the susceptible organisms or by determining the rate of depolymerization of the substrate isolated from the susceptible organism by the viscosimetric method of Meyer<sup>7</sup>.

Meyer has further shown that the lysozyme concentrations are very high in the gastric juice of patients with peptic ulcer and in the stools of patients with chronic ulcerative colitis<sup>3,4</sup>. He has demonstrated that lysozyme will digest mucus and postulates that the destruction of the protective coating of the bowel exposes the underlying mucosa to the action of noxious agents of the intestine such as hydrochloric acid or the indigenous bacterial flora. These postulates he has substantiated in part by feeding lysozyme to dogs and thus producing acute ulceration of the upper gastro-intestinal tract<sup>8</sup>.

Because of these findings, it seemed profitable to explore variations in lysozyme concentration in the stools of human subjects under a variety of circumstances and life situations.

**Method.** All tests were done according to the viscosimetric method of Meyer.

The specimens of wet stool were extracted with 0.1 normal hydrochloric acid (2 gm. of stool per 10 cc. of 0.1 normal HCl) within a few hours after their passage and stored in an ice box at 4°C. Just prior to carrying out the assay, appropriate dilutions of the extract were made with normal saline so that half viscosity would be reached within 30 minutes.

As far as possible, all specimens from the same subject were assayed on the same day, using the same substrate.

The substrates used had a relative viscosity close to 3.5, and the one sample which was standardized by comparison with a sample of purified lysozyme obtained from Dr. Karl Meyer was accurate within 2%, the approximate range of error of the method at this level of viscosity. At viscosity readings higher than 50, the method is accurate within 3-4%.

Stool specimens, both random and 24-hour samples, were analyzed. They were obtained from subjects with a variety of disease states as well as from normal subjects. In the case of two subjects, secretions obtained directly

from the surface of the exposed intestinal mucosa were studied.

In addition, day to day determinations were carried out on specimens from a series of patients with ulcerative colitis and mucous colitis, as well as from a series of normal subjects. On each subject, a diary was kept which contained data relating to events in the life situation, emotions, attitudes and feeling states. The day to day observations were then correlated with symptomatology referable to the colon and also with other bodily complaints and the general level of well being.

Finally, the effect of the application of lysozyme to the human colon was studied.

**Results.** The range of lysozyme concentration observed among all the groups of subjects are summarized in Table 1.

**NORMAL SUBJECTS.** Healthy individuals without complaints were regarded as normal subjects. Among these individuals, lysozyme concentrations were uniformly low during times of relative calm and security. Figures ranged from 0.3 to 1.7 units per gram of wet stool. In a subject with acute congestive heart failure, the lysozyme concentration was likewise quite low (1.2).

Two subjects who were studied daily were normal except that they were prone to develop diarrhea in circumstances of anxiety and apprehension. In these subjects, as detailed below, there occurred a rise in lysozyme concentration which was small, but definite, and was noted during the time of anxiety and apprehension and the associated diarrhea. In a third subject, studied daily, there was noted a rise in lysozyme during a period of anger and resentment, unassociated with any change in bowel function.

**CASE 1.** One of these subjects was a 26 year old white male who 2 years previously had had a mild episode of ulcerative colitis from which he made a complete symptomatic recovery. Roentgen-ray and sigmoidoscopic examination were unremarkable. During periods of relative security and relaxation, stool concentrations of lysozyme were found to range between 0.3 and 0.8. During a period of anticipation of returning to visit

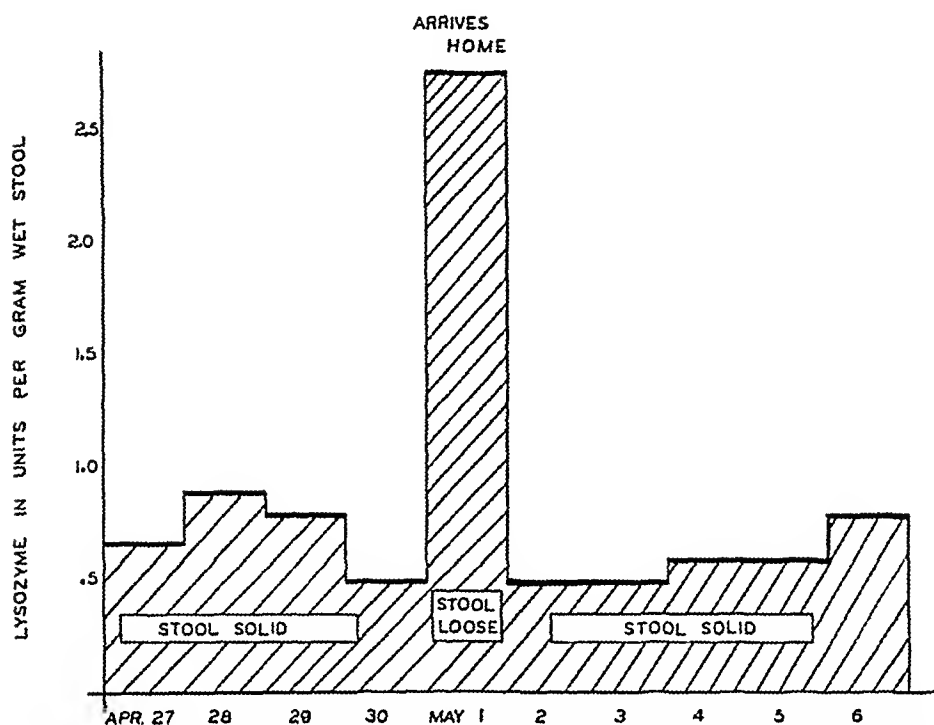


FIG. 1.—Transitory marked rise in lysozyme concentration in the stool associated with anxiety and conflict (Case 1). All assays of the stool specimens were carried out on the same substrate on the same day.

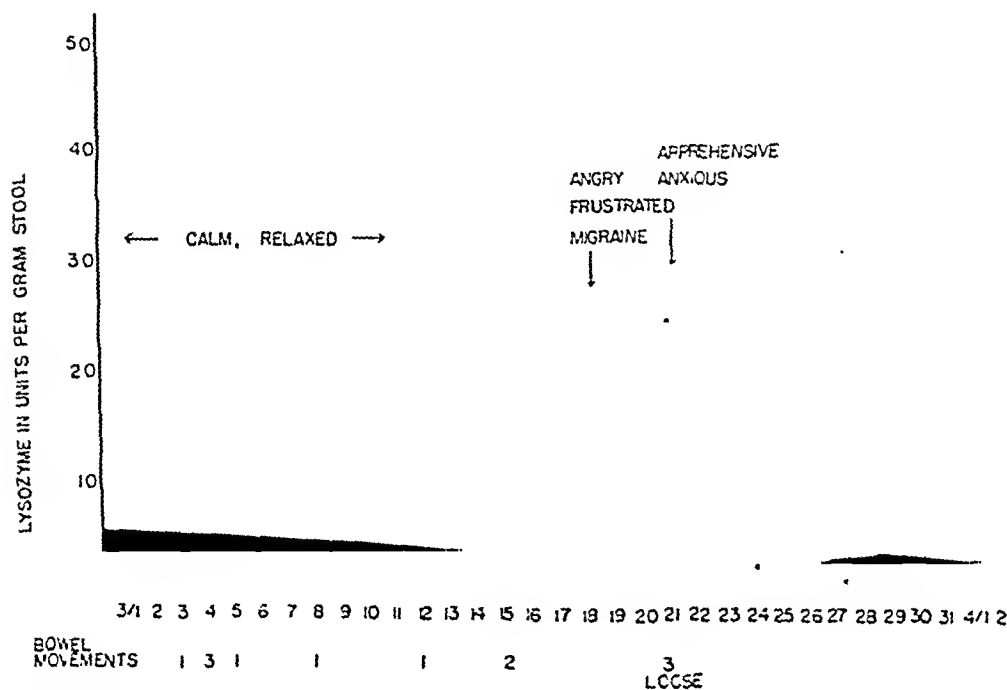


FIG. 2.—Abrupt rise of lysozyme concentration associated with loose stools in a normal male (Case 2). All determinations were performed on the same substrate.



his parents and presenting to them a young woman whom he hoped to marry, he developed diarrhea and a concomitant rise in lysozyme to 2.8. Later, when he was comparatively secure and relaxed, the values fell again to 0.5 (See Figure 1).

CASE 2. Another subject was a 32 year old married physician, also inclined to develop diarrhea in situations productive of anxiety, insecurity, guilt and resentment.

On days of relative calm, security and self-assurance, the lysozyme stool content was low (0.4 to 0.6 units per gm.). During a period of increasing anger, hostility and resentment over a series of frustrating episodes associated with his experiments which precipitated a migraine headache, the lysozyme concentrations gradually rose to 1.2 units per gm. On the day following an acute episode of apprehension and anxiety over the presentation of an ill-prepared case at a conference, the concentration of stool lysozyme rose to 2.5 units. On subsequent days of calm and relaxation, the lysozyme concentration again fell to and remained at low levels (See Figure 2).

CASE 3. A 54 year old white male had undergone 13 years previous to our studies a "double barrel" colostomy because of a rectal stricture secondary to lymphogranuloma venereum. Shortly after the operation there occurred and persisted a large prolapse of descending and sigmoid colon through the stoma. He was otherwise healthy, however, and at the time of study his colonic mucous membrane was of essentially normal appearance. Specimens of mucus were obtained directly from the exposed bowel.

Usually he was relatively relaxed and self-assured. At such times the values for lysozyme concentration of the bowel secretions were low (0.1 units per gm.). Following an episode of questioning, however, when he mistakenly thought he was being looked upon as a homosexual, he reacted violently, with anger and bitter resentment persisting for 2 days. During this period, the lysozyme concentration rose to 10.8 units per gm. Subsequently, but only with vigorous reassurance, he became calm and relaxed again, and the lysozyme fell to lower figures (2.8 and 0.4 units per gm.). See Figure 3.

Comment. From these data, it would appear that in normal subjects there may occur a rise in colonic lysozyme concentrations in response to situational threats productive of anxiety and apprehension and during periods of anger, hostility, and resentment. The increase in lysozyme concentration in

these subjects was not of great magnitude, however; neither was it sustained over a period of days. Being thus of minor degree and transitory, it was probably of little importance to the welfare of the individual.

(2) PATIENTS WITH ULCERATIVE COLITIS. In a series of 12 patients with ulcerative colitis in a state of remission, with minimal symptoms and enjoying feelings of relative relaxation and security, the stool lysozyme concentrations were low (0.7 to 1.6 units per gm.). In 4 patients with ulcerative colitis whose symptoms were mild, stool concentrations varied from 13-25 units per gm. In 3 subjects with ulcerative colitis whose symptoms were moderately severe, concentrations of stool lysozyme varied from 40 to 100 units.

In subjects with ulcerative colitis in whom day to day observations were made, lysozyme concentration was low during remissions which coincided with periods of relative self-assurance and security. During exacerbations, however, usually marked by situations provocative of unexpressed anger, hostility, and resentment, there occurred sharp rises in stool lysozyme. In fact a sustained, marked elevation of lysozyme concentration usually presaged a period of bloody diarrhea, as illustrated by the following protocol.

CASE 4. A 36 year old graduate nurse had had bloody diarrhea for 4 years. Repeated sigmoidoscopic examination, Roentgen-ray and stool examinations for pathogenic organisms supported the diagnosis of ulcerative colitis. The patient was a rigid, immature, insecure, obsessive, compulsive personality, almost completely unable to express either hostile or warm feelings. Marital life had been characterized by persistent turmoil, chiefly over difficulties with her in-laws and differences with her husband. In Fig. 4 are summarized the findings in her case.

The initial low figures were obtained during times of relative calm, security, relaxation, and smooth environment. Just before the first rise, a control specimen showed a value of 2.5 units per gm. The following afternoon

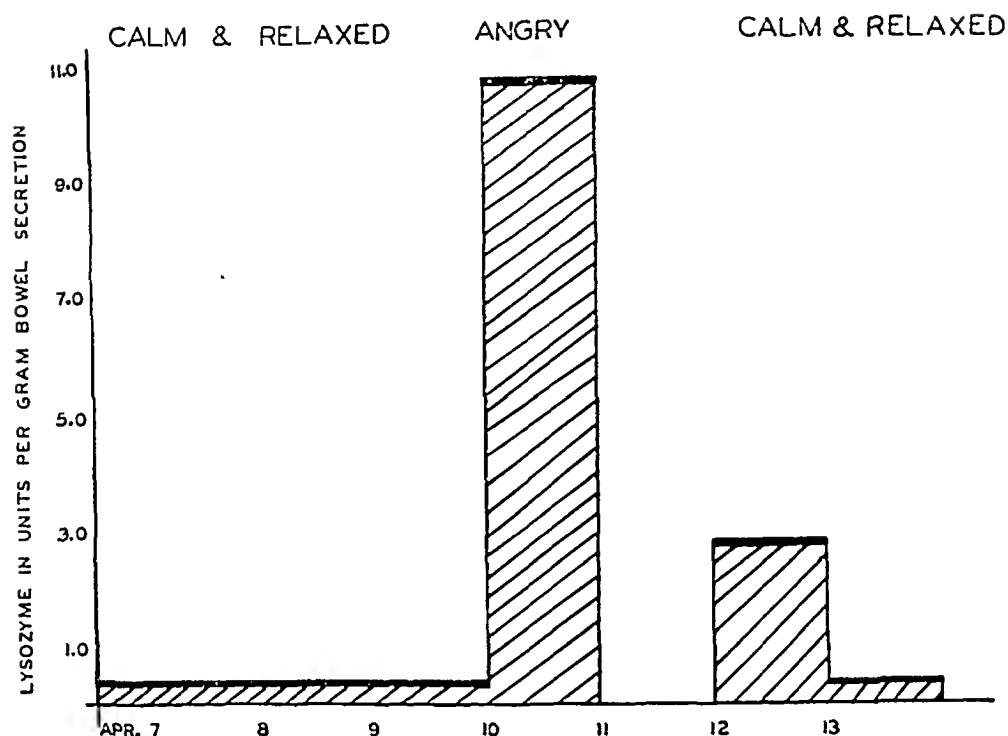


FIG. 3.—Variations of lysozyme concentration in the colonic secretions of a fistulous subject (Case 3) with marked increase during anger and resentment. All specimens were assayed using the same substrate.

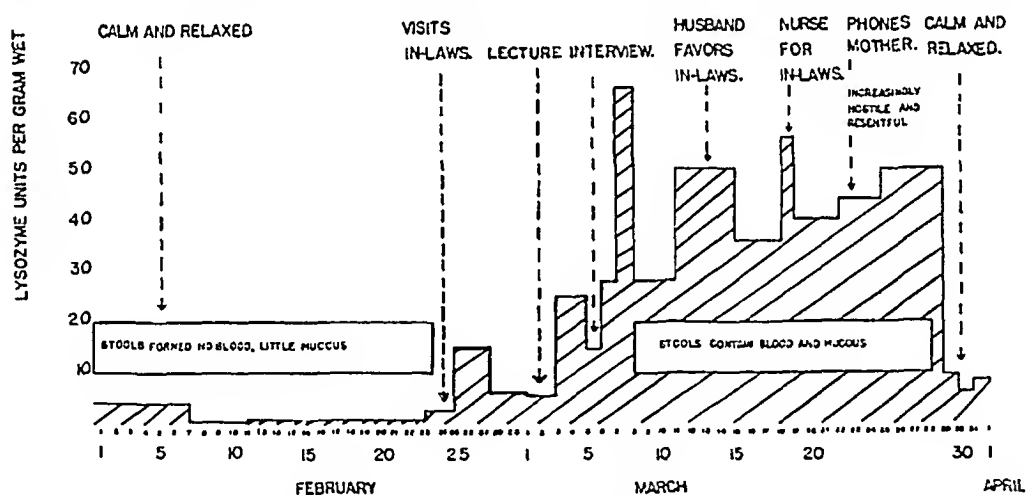


FIG. 4.—Case 4. Correlation of lysozyme concentration with situation, attitude and symptomatology in a subject with chronic ulcerative colitis. All determinations performed on the same sample of substrate.

was spent visiting her in-laws, whom she hates and blames for most of her difficulties, but toward whom she is unable to express verbally or act out her resentment. By the following day the lysozyme concentration had risen to 14 units per gm. Six days later, the value fell to 5 units per gm. The patient spent March 1st attending a lecture on psychoanalytic interpretations of aggression. She knew her husband would object to this, and she felt considerable guilt over it. She hurried home to prepare his dinner, and faced him that evening with mixed feelings of

guilt, hostility, and resentment. The following day, the lysozyme concentration rose to 25 units per gm. There was no exacerbation of symptoms on this occasion.

During the next few days she gradually became more calm and concomitantly the lysozyme concentration fell to 14. On March 1st she had an interview with a member of our staff whom she thought was a psychiatrist. The interview upset her considerably, as she felt that he could easily "see through" her defenses. She was quite disturbed and angry, and she felt humiliated. She rushed

blindly from the office, and was half-way home on the train before she could compose herself. The following day the lysozyme had risen to 66 units. She was having moderately severe abdominal cramps on this and subsequent days, and the stools were grossly bloody. By the 8th of March the patient had somewhat regained her composure, and the lysozyme was 28 units. During the period of March 10 to 15 the patient's husband began to make plans to provide for a vacation for his parents, and the plans were culminated by the patient, her husband and in-laws spending a week-end looking for a hotel for the in-laws. During this period, she was becoming more and more bitter, angry and resentful, but kept her feelings to herself. The crowning blow was the husband's announcement that he and the patient could not afford to take a vacation and that furthermore, he was planning to provide a practical nurse for the parents. Recalling that when she was severely ill and hospitalized with ulcerative colitis the husband had never proposed providing her a nurse, she became violently angry, resentful, and hostile and the lysozyme, which had fallen to 36, rose again to 57 units. At this time, she was having only one bowel movement every 2 or 3 days, but these stools were accompanied by considerable mucus and blood. The next week-end the patient placed a long overdue telephone call to her parents in Montreal with mixed feelings of guilt and anxiety. During the conversation, her husband stood over her with a stop-watch and sharply reminded her when her time was up. At this she again became angry, resentful, and hostile. She took no aggressive action, however; maintained a cool exterior but inwardly seethed with anger for the next few days. The lysozyme concentration in her stools, which had begun to decrease, rose again during the remainder of the week to 40, 44, and 50 units per gm., and constipation became more pronounced. However, the following week, after unburdening herself of some of these hostile feelings to her doctor, she gradually regained relative serenity and her bowel movements became regular and daily, and the blood disappeared. By this time lysozyme had fallen to low levels of 9, 6, 8, and 7 units per gm.

CASE 5. A 26-year old white male automobile mechanic had had ulcerative colitis for 6 years. Shortly after the onset of symptoms he was treated surgically by cecostomy, and later, 4 years before he was seen at New York Hospital, by ileostomy. Two years after the ileostomy a fistula developed through the old cecostomy wound. A loop of ascending colon evaginated through this defect and lay

exposed on the surface of the abdomen. Specimens of mucus secretion from the surface of this loop were examined daily for lysozyme and correlated with the amount of secretion, the contractile state of the bowel, feeling states, attitudes, general behavior, and life situation. During times of relaxation and security, lysozyme values were low, ranging from 14 to 35 units per gm. On days of hostility, anger and resentment, lysozyme concentration in the secretions was markedly elevated (80 to 100 units per gm.). At such times it was often possible by reassurance, and by allowing the patient to express freely his feelings, to effect a significant fall in lysozyme concentration. There did not appear to be a direct relationship between the amount of mucus secretion and the concentration of lysozyme in the mucus. At times they were both increased, both decreased or one increased and the other decreased. In Figure 5, lysozyme values are correlated with variations in attitudes and emotional reaction.

It is apparent that situations associated with relative calm and security correspond with relatively low lysozyme titers in the neighborhood of 15 to 25 units per gm. of secretion. Situations associated with anger, hostility, guilt, and resentment, on the other hand, were associated with increased lysozyme production of 80 to 100. One such humiliating episode occurred when the patient, an extremely fastidious person, was allowed to sleep late, then brusquely awakened and sent to the laboratory without affording him time to wash, shave, or change his dressing. He characteristically took pride in having a clean and neat dressing. When he arrived at the laboratory, he was angry, irritable, and very resentful about being placed in such an embarrassing position. His lysozyme concentration was accordingly elevated to 80 (March 4th). On another day the patient was to be sigmoidoscoped (March 2), a procedure which he dreaded, because of unpleasant past experiences. The prospect irritated him and he felt anxious and apprehensive over it. Associated with this reaction the lysozyme was 67. On another occasion, the patient arrived at the laboratory fuming with anger. He had just received news that his sister-in-law was about to move back into his house. He objected to this violently, and felt that his brother was "putting something over on him" while he was in the hospital. A specimen obtained at that time contained 80 units of lysozyme (March 13). A few days later, he was visited by his sister-in-law. In order to avoid unpleasantness in the ward, he was "nice" to her, although he was seething inwardly. On this occasion, the lysozyme was 100 (March 15). These high levels con-

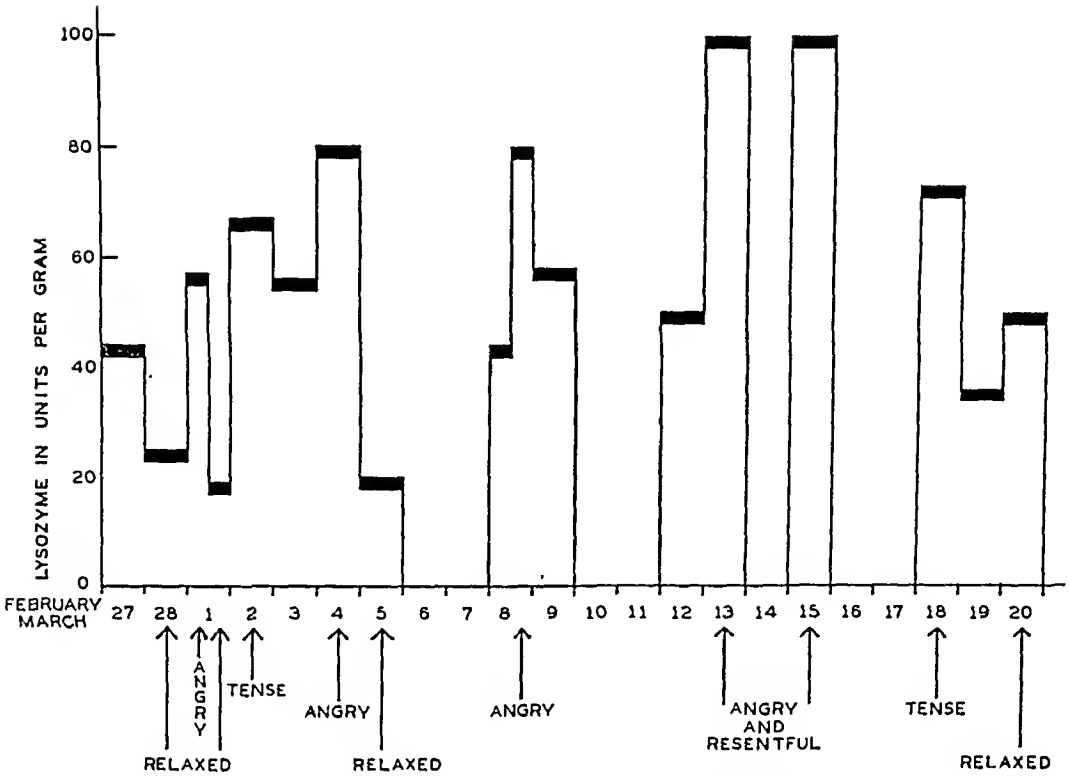


FIG. 5.—Case 5. Correlation of feeling states with day to day variations in lysozyme concentration in the secretions removed from the surface of the exposed bowel.

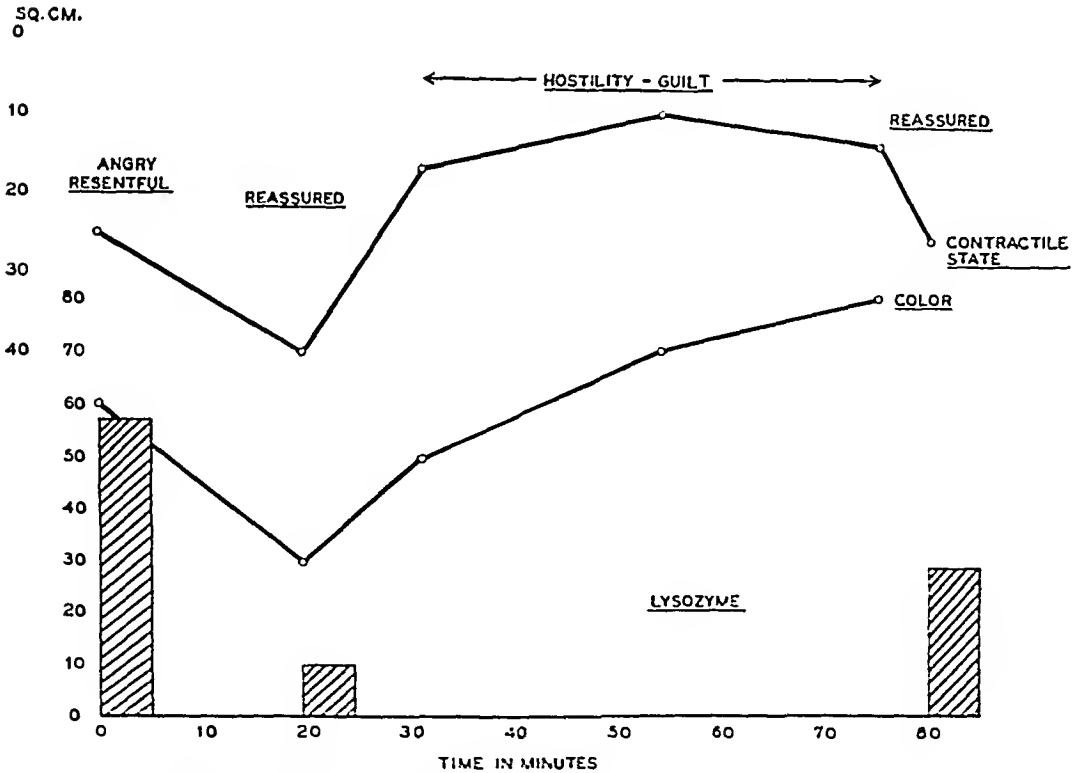


FIG. 6.—Case 5. Variations in lysozyme concentrations in the secretion of the exposed bowel in the interview situation on a day when the patient was angry, resentful and hostile.

trast strikingly with the comparatively low values of 19, 20, and 36 when the patient was relatively content, secure, cheerful, and relaxed.

Figure 6 shows the variation in the lysozyme concentrations during the following experimental situation, which included an interview, at first reassuring, and then traumatic:

On arriving at the laboratory, the patient was irritable, angry, and hostile because three doctors had come to his bed, removed his dressing, and, after merely examining his colon, had walked away without speaking to him. He said that he felt like a "freak", and was going to "sign out" of the hospital. Lysozyme concentration in the secretion following this episode was 57 units per gm.

After about 30 minutes of reassuring discussion and ventilation, he felt more relaxed, and within a few minutes the lysozyme concentration had dropped to 10 units. The discussion was abruptly switched to certain events in the patient's life about which he was in great conflict. He spoke of them with poorly concealed feelings of hostility, resentment, and guilt. At the end of the interview, the lysozyme concentration had risen to 33.

In contrast to this ready variability in lysozyme concentration was the relatively fixed situation on another day. On this day, the patient was relatively secure, calm, and relaxed. The interviewer was unsuccessful in his attempt to elicit any evidence of feelings of guilt, hostility, or resentment, even though topics usually sensitive were discussed. Rather did the patient seem reassured by the opportunity to unburden himself of his conflicts. Lysozyme concentration fell from an initial level of 25 to a level of 14 at the end of the interview.

A third interview situation is represented by Figure 7.

The patient arrived at the laboratory quite cheerful and in good spirits. During the interview, previously concealed topics of significant conflict were uncovered. Discussion of them was fraught with embarrassment and discomfort on the part of the patient as well as with considerable feeling of resentment and hostility. The initial lysozyme value of 19 gave way to 33 at the end of the interview.

(3) **LYSOZYME IN MUCOUS COLITIS:** In 6 patients with mild mucous colitis, both those with diarrhea and those with constipation, lysozyme concentration was low (0.4 to 1.5).

In one subject with moderately severe constipation and mucous colitis, lysozyme concentration was in the

neighborhood of 25 during times of anger, hostility, resentment. During periods of relative security, lysozyme in the stool fell to lower levels. One subject with mucous colitis displayed fairly marked changes in lysozyme concentration which corresponded to changes in symptomatology and life situation.

CASE 6. A 36 year old negro chorus girl, in a setting of realization of her inability to compete with younger women, frustration at being unprepared to do any other type of work, and bitter resentment about her lot in life, developed watery diarrhea with cramps and the passage of mucus. A specimen taken when she was first seen in the clinic, at which time she was complaining chiefly of constipation, and had developed a fissure-in-ano, showed a relatively high lysozyme titer of 27 units per gm. At a later date, following several interviews in which she was encouraged to express freely her feelings and was given strong reassurance and moral support, the lysozyme fell to 14 units.

Later, she was hospitalized on the gynecological service because of irregular menses. After 3 days in the hospital being prepared for operation her menses began, so she was discharged without operation. She resented the loss of 4 days of work and felt that nothing had been accomplished. She did not express her hostile feelings, but concomitantly stool specimens contained lysozyme in a concentration of 25 units per gm.

At a later period, during a time of considerably more peace of mind consequent upon obtaining a new job and being paid by the union for her lost time, the lysozyme concentration fell to 8.5 units per gm. (See Fig. 8).

(4) **LYSOZYME IN CARCINOMA OF THE COLON:** The possibility that ulceration itself might provoke an elaboration of lysozyme was further tested by analyzing the stools of a subject with an ulcerated carcinoma of the colon. Lysozyme concentration was, however, persistently low (3.2).

(5) **RELEVANCE OF LYSOZYME CONCENTRATION TO TISSUE DAMAGE:** Attempts to assess the effects of lysozyme applied to the intact colonic mucosa were made in the case of the subject described above (Case 3), who was healthy except for a colostomy through

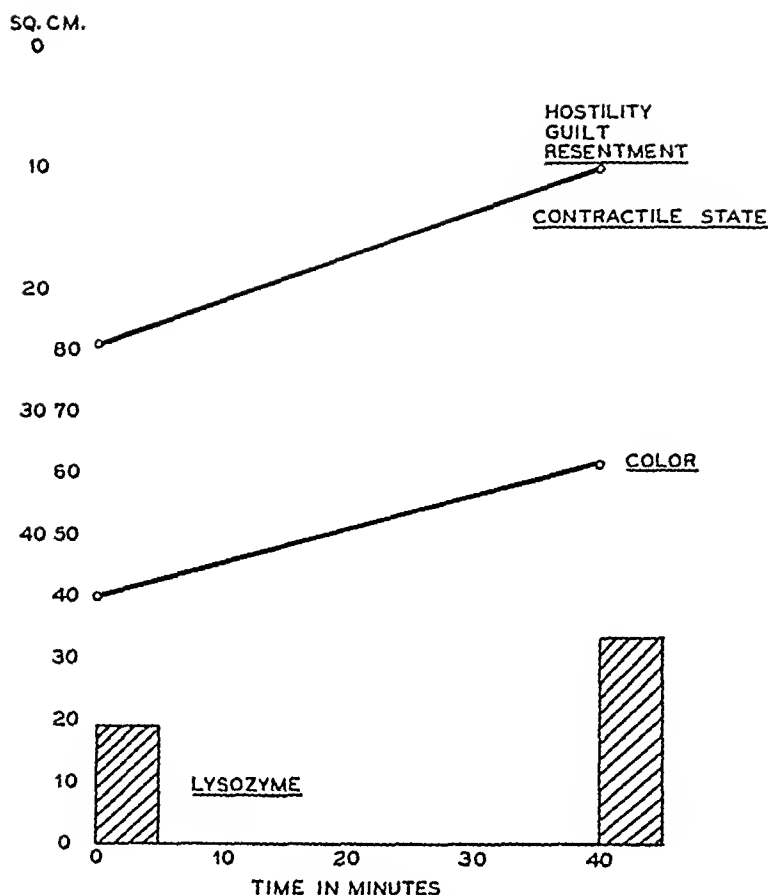


FIG. 7.—Case 5. Hyperemia, hypermotility of the colon and rise in lysozyme concentration associated with feelings of hostility, guilt and resentment. Color values were obtained by direct comparison under standard lighting to a Tallqvist hemoglobin scale standardized by the method of Munsell. The figures representing contractile state were obtained from direct measurement of the length and width of the exposed loop of bowel.

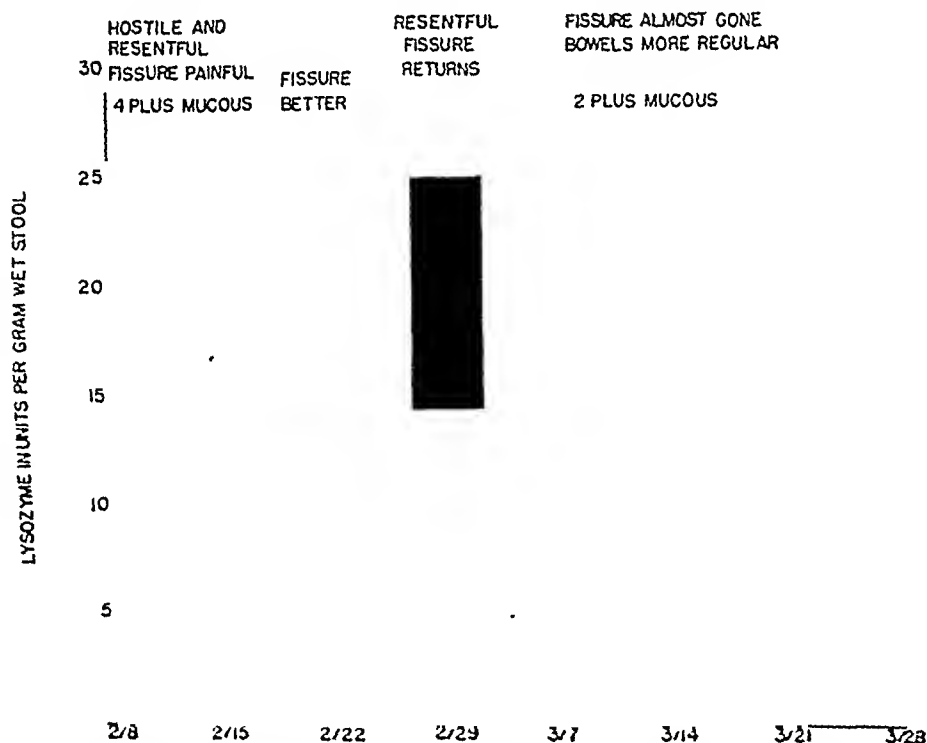


FIG. 8.—Case 6. Correlation of feeling state with lysozyme concentration and mucus in the stool of a subject with severe mucus colitis. All specimens determined on the same day and on the same substrate.

which had herniated a large segment of sigmoid colon.

Human tears containing lysozyme in a concentration of 600 units per cc. were applied to the surface of the bowel on small cotton pledgets and allowed to remain in place for 24 hours. At the end of this time, in 3 of 4 such experiments, a small, sharply circumscribed area of inflammation and edema was noted at the point of application. Control applications of normal saline, boiled tears and dry cotton failed each time to produce any lesion.

*Comment:* The fact that unboiled tears are capable of bringing about injury to the mucous membrane of the normal human colon, while boiled tears and saline fail to do so, suggests that the lysozyme may be responsible for damaging the colonic mucosa, or, by removing the protective mucus coating, for exposing the mucosa to injury from trauma or infection. This finding in humans is in keeping with the data of Meyer in which intestinal ulcers were produced in animals by feeding lysozyme. An analogous situation had been produced in cats by Rappaport and Nauss,<sup>13</sup> who found that the colon, damaged by chemical agents was much more susceptible to the invasion of *Entamoeba Histolytica*. It is possible that in humans the mucolytic action of lysozyme allows amebae as well as other noxious agents freer access to the cells lining the wall of the bowel.

That lysozyme is not the result of ulceration in the bowel is established by finding it in high concentration in the stools of patients who have no ulcerations in their intestine, as well as by finding variations in lysozyme concentration in the secretions removed from the surface of the intact mucosa. Likewise, low values were found in the stools of patients with ulcerating neoplastic disease of the large intestine. Moreover, in the subjects with ulcerative colitis described above, the rise in

colonic lysozyme antedated the onset of bleeding and other symptoms.

**Summary and Conclusions.** The concentration of the mucolytic enzyme, lysozyme, has been measured in the stools of normal subjects and subjects with mucous and ulcerative colitis under a variety of circumstances and associated with widely varying life situations, emotions and attitudes. It was found that among normal subjects and subjects with diarrhea without ulceration, transitory elevations of lysozyme often occur in company with general reactions of humiliation with anxiety, resentment and guilt. Among subjects with ulcerative colitis, on the other hand, marked and sustained elevations of lysozyme were observed in such situations. These periods were characteristically marked by feelings of intense anger and hostility which were

TABLE 1.—THE RANGE OF CONCENTRATION OF LYSOZYME IN STOOL SPECIMENS IN VARIOUS DISEASE STATES AND IN NORMAL SUBJECTS.

	Units per gm. Wet Stool
Normal Subjects	0.3— 1.7
Acute Congestive Heart Failure	1.2
Cancer of the Large Intestine	3.2
Mucos Colitis, (Mild Cases)	
A) Constipation	0.6
B) Diarrhea	0.4— 1.5
Ulcerative Colitis	
Remission	0.7— 1.6
Mild Symptoms	13. — 25.
Mod. Severe Symptoms	40. —100.
Regional Enteritis, Remission	0.4— 0.8
Acute (24 hour) Gastroenteritis	0.7

unexpressed and repressed with varying degrees of completeness, so that the subject displayed an exterior of relative calm and "sweetness". Such elevated values for lysozyme in the stool contrasted with relatively normal values in the same subjects during periods of satisfaction and contentment. Moreover, the high values were found immediately to precede episodes of exacerbation of symptoms with bleeding.

It is concluded from these data that lysozyme concentration in bowel secretions is highly relevant to the occurrence of ulceration, and that furthermore, variations in the production of lysozyme correspond to variations in the state of security of the organism as a whole. When the individual was

meeting threats to his security arising out of problems of day to day adjustment with feelings of humiliation, guilt, anger and hostility, but was repressing them to present a serene and non-aggressive exterior, an excess of colonic lysozyme was likely to be elaborated.

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# TREATMENT OF POLIOMYELITIS INVOLVING THE RESPIRATORY SYSTEM

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IN 1946, 1283 cases of poliomyelitis were admitted to the communicable disease division of this hospital; in 1947, 392 cases. Many respirator cases required tracheotomies. Standardization of treatment in such cases seemed desirable and the following plan was used in the management of cases of acute bulbar poliomyelitis requiring tracheotomy while in the respirator. The discussion merely presents practical considerations in the care of these patients.

**INDICATIONS FOR TRACHEOTOMY.** The first question raised in treatment is: will tracheotomy benefit the patient? The next question is: when should it be performed? In the absence of an oximeter to determine when the patient actually is hypoxic, the following criteria for tracheotomy were established: 1. Definite bulbar signs, usually a nasal voice and signs of interference with swallowing, the mucus pooling in the throat and posterior pharynx, endangering a free air-way. 2. Bulbar or spinal types which at first appear to be doing well, but which gradually show increasing anoxia, either in or out of a respirator. Cyanosis *per se* is often not demonstrable. Useful criteria of hypoxia are increasing pulse rate, headache and restlessness despite what appears to be an adequate respiratory exchange. 3. Atelectasis. 4. Paralysis of the vocal cords.

The advantages of tracheotomy are: the easy removal of mucus from the respiratory tract; an adequate oxygen tension is more easily maintained; emergency life-saving bronchoscopy can be performed through the wound even with the patient in a respirator; pulmonary edema may be treated more easily with positive pressure; it is unnecessary to force the patient's mouth open, sparing the patient an upsetting procedure.

Early performance of tracheotomy is stressed. If the operation is performed before any emergency sets in, the patient may be bronchoscoped, mucus removed, oxygen supplied through the bronchoscopy tube, and a more leisurely tracheotomy performed over the tube.

It often becomes necessary to do a tracheotomy on a patient who may only breathe within a respirator; in such cases, the so-called "stab" tracheotomy may be life-saving, but it should not be allowed to become necessary. Positive pressure, just as used in anesthetic procedures, may be used to carry the patient on forced breathing, during which he may be removed from the respirator and the tracheotomy carefully performed. It is desirable to have as high a tracheotomy as possible. Subsequent treatment is simplified in that the tracheotomy tube will be well out of the respirator when the collar is

in place. Pneumothorax and subcutaneous emphysema should be avoided. With trained assistants present the patient may be replaced in the respirator in about 1 minute after the tracheotomy tube is in place.

**MANAGEMENT OF PATIENT IN RESPIRATOR.** Once the tracheotomized patient is in the respirator continuous care by nurses trained in the management of respirator patients is of the utmost importance and the following treatment is carried out with variations to meet individual requirements. All necessary equipment essential for handling any emergency that arises must be in the immediate environment of the patient. This includes a reserve oxygen tank, a dependable suction machine with a cord long enough to prevent tension from being placed on the electrical outlet connections, rubber catheters with a few small openings around their tips and one particular catheter with an open end for removing mucus plugs. Catheters should be small enough to pass through tracheotomy tubes without applying undue force. Catheters carrying oxygen to the larynx should have numerous openings: they become plugged very quickly. The oxygen line should be supported so that it will not kink. A Wangenstein suction apparatus should be present: when needed, it is always because of emergency. Bronchoscopic equipment should be near by and a bronchoscopist available.

During the acute phase, the respirator is tipped with the head down. The angle should be steep enough to insure drainage of the bronchial tree. Shoulders should be well padded. Mucus is removed by gentle suction through the tracheotomy tube to maintain an unobstructed air-way. Normal saline containing 200 units of penicillin per ml. is instilled, prior to suctioning, a few drops at a time into the tracheotomy tube.

If the patient becomes cyanotic de-

spite adequate suctioning, perform bronchoscopy. Some patients may require bronchoscopy 3 or 4 times in 24 hours. Penicillin is given routinely, generally 30,000 units intramuscularly every 3 hours. Oxygen passed through cool water is allowed to flow into the tracheotomy tube at the rate of 2 or 3 liters per minute. Oxygen-helium may be used for short periods. A Levine tube is passed early to facilitate administration of fluids and provide means of emptying the stomach if gastric dilatation occurs, as frequently happens. Prompt treatment can be a life-saving measure.

A properly fitted collar is very important. The back of the patient's neck should be protected by using very soft material. To keep the tracheotomy tube within easy reach of the nurse, use a metal shield which forces the sponge rubber collar forward into the respirator, and pack the resulting space around the patient's neck with towel-ing.

Nothing is offered orally while the patient is acutely ill. Careful attention is paid to the fluid intake. The type of fluid given is guided by blood chemical determinations. Serum chloride is checked frequently among other things: low values have been noted and are due to constant loss from many causes. Whole blood is given when needed. As a rule fluids are given intravenously for the first 4 or 5 days; occasionally the subcutaneous route is used. Intravenous amino acid preparations may be used to supply protein. Vitamins are given in customary dosage.

When sedation is required, chloral hydrate is usually given by rectum. Potassium iodide is used routinely to keep secretions less tenacious.

The speed of the respirator must be watched constantly and not be allowed to exceed 18 times a minute. *Respirators tend to run much too fast.* The pressure measured in centimeters of

water is kept between negative 16 to 18 and positive 3 to 5: children are carried at 12 to 15 negative and about 3 positive.

If the patient is unable to synchronize his breathing with the respirator, curare is used to paralyze those respiratory muscles which are receiving occasional aberrant motor impulses from the respiratory center, so that the patient will breathe only with the respirator. Synchronization of the patient and respirator is vital in the treatment of respirator patients. A dose of 1 to 2 cc. of intocostin by the intramuscular route is preferred. One or 2 doses usually suffice, but more may be needed.

Generally when an acutely ill patient is placed in a respirator, hot packs to the chest or extremities are discontinued if the patient's fever is high. All physiotherapy is withheld the first few days. The patient should rest as much as possible. At times the nurse must keep the respirator continuously closed, using the arm ports to care for the patient's bodily needs.

Every encouragement possible is given the patient. Immediate members of the family are constantly warned against doing or saying anything which might conceivably upset the patient. Morale is an important factor in recovery.

A sincere attempt is made to segregate the new acutely ill patient from other cases which have the first few days of their illness behind them. One must guard against any possible secondary respiratory infection. Personnel as well as patients are constantly checked.

As the patient's condition improves hot packs and physiotherapy are started. Roentgenograms of the chest are taken when indicated. White blood counts and hemoglobin determinations are done at least 3 times a week. Frequent urine examinations are made. Urinary tract infections are usually

treated with sulfadiazine and sulfamerazine in equal parts, when a retention catheter is considered necessary, it should be employed promptly. Enemas, and occasionally prostigmine are used to overcome distention. Blood pressure and pulse are watched constantly.

As improvement continues, a high-caloric, high-protein diet is started. As a rule it is fed through a Levine tube. Amounts are increased gradually depending on the patient's tolerance. In 8 to 10 days the patient usually receives nearly all fluids orally. Acute cases showing rather severe paralysis of the chest and extremities at onset, frequently improve remarkably within a few days. This may be due to subsidence of edema in the spinal cord. One should make every effort to get such patients out of the respirator at the earliest possible moment. Other patients are placed on a definite removal schedule according to the improvement of their condition: it may be only a minute or two out of every hour but one should attempt to lengthen the time a little each day. It is of the utmost importance for the physician to gain the patient's confidence.

Everyone working with the patient should be fully aware of all problems connected with his case. Experience has shown that when an emergency occurs in any certain patient, this same emergency may be repeated many times. Everyone should know how to handle the problem. All personnel should be cautioned to form the habit of constantly checking the pressure gauge on the respirator; it takes only a fraction of a second and may be life-saving.

As the patient improves, oxygen administration is decreased gradually and finally discontinued. Following this, if the patient's condition remains satisfactory over a period of 24 to 48 hours, the tracheotomy tube may be closed off

but not removed. One week after the patient has tolerated a closed tube it may be removed. On 3 occasions a second tracheotomy had to be performed. All were due to upper respiratory infection after the first tracheotomy had healed. These patients could not cough up secretions, the mucus became inspissated, plugs formed, atelectasis followed, and the whole procedure had to be repeated.

Above all, patience and tolerance on the part of doctors and nurses are essential. It is, in many instances, a long hard battle but one which is being increasingly won.

In 1946 we treated 129 cases of bulbar poliomyelitis, with 38 deaths including one resulting from polio-encephalitis. Tracheotomies were performed on 14 of the above patients, out of which number there were 7 deaths. In 1947 we performed 8 tracheotomies with 4 deaths. Of the 14 tracheotomies in 1946, all but one were respirator cases.

Except for individual variations the above is the treatment now used. It will undoubtedly be improved with additional experience, but during 1946

and 1947 it saved about 50% of patients of a type that previously died.

**Summary and Conclusion.** 1. The management of patients suffering from poliomyelitis with respiratory involvement requiring the use of a respirator has been presented.

2. The indications for, and the type of tracheotomy preferred, have been described. The value of performing an early tracheotomy has been stressed.

3. Prevention of mechanical difficulties which arise from time to time in the management of patients suffering from acute poliomyelitis and in a respirator, cannot be over-emphasized. Adequate nursing care is essential.

4. In our opinion, the treatment described here definitely has reduced mortality at least 50% in cases of acute bulbar poliomyelitis in the respirator and having had a tracheotomy performed.

By October 20, more than 2300 cases have occurred in the present epidemic. Of 248 bulbar cases over 60% have had tracheotomies performed. Early tracheotomy cannot, in our opinion, be over-stressed in the management of acute bulbar poliomyelitis. Actual statistics must await the end of the current epidemic.

# THE EFFECT OF THERAPEUTIC DOSES OF ASPIRIN ON THE ACID-BASE BALANCE OF THE BLOOD IN NORMAL ADULTS\*

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RECENT studies on the effect of salicylate administration on the acid-base equilibrium of the blood have presented conflicting results. Fashena and Walker<sup>6</sup> concluded that a metabolic acidosis occurred in children receiving salicylates. In contrast, Rapoport and Guest<sup>7,11</sup> reported a respiratory alkalosis in children and animals. Reviews of previous work may be found in these papers.

As Erganian and co-workers<sup>5</sup> pointed out, the differences in results and interpretations may be due to differences in experimental subjects: "An attempt is made to compare results on anorexic younger children and infants with experimental results obtained on older children, adults, and even animals, whose usual caloric and liquid intakes have not been affected prior to or during the period of study." Also, differences in doses, time and duration of administration of the drug, and chemical determinations that were inadequate to permit complete characterization of the acid-base balance contributed to the conflicting results. Furthermore, no quantitative estimates of respiratory changes have been reported;

nor have the possible side-effects of nausea, vomiting, anorexia, starvation or renal compensatory factors on the acid-base equilibrium been considered.

Because of the discrepancies mentioned, and because no studies on adults are available, it was decided to study the time relations of the effects of therapeutic doses of aspirin on the acid-base balance of the blood in normal adults and the possible pathways of displacement and recovery.

**Experimental Procedure. SUBJECTS.** The subjects were 10 healthy adult males, the majority of whom were in their 20's and 30's, with an average age of 26.3 years. The youngest subject was 14 years old and weighed 149 lbs. None of the subjects had any history of allergy or aspirin sensitivity.

**EXPERIMENTAL METHODS.** Resting values of all measurements for each subject were determined before medication was begun. Each subject was then given 1.3 gm. of aspirin by mouth every hour for 8 doses and 1.6 gm. at the 9th hour, making a total of 12 gm. This is one of the higher dosages recommended in the treatment of rheumatic fever.<sup>2</sup>

Determinations of the serum salicylate level,  $V_c$ , serum pH, total  $CO_2$ , content of the blood, respiratory volume in liters per minute and respiratory rate per minute were done every 2 hours for 16 hours† and again at the 28th hour. The temperature and blood pressure

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† In preliminary experiments, blood samples were drawn at 1-hour intervals. Since the changes were within the limits of the experimental error of the method, the 2-hour schedule was adopted.

were determined at the same time intervals.

The subjects remained in bed during the course of the experiment, except for bathroom privileges. Water was allowed freely. During the experiment subjects were given a low-fat diet in order to facilitate the colorimetric determination of serum salicylate levels.

Estimates of the acid-base equilibrium were made on samples of finger blood. The micro technique of Shock and Hastings<sup>13</sup> was followed for the determination of per cent red cells ( $V_c$ ), the pH of the serum at 38°C ( $pH_s$ ), and the total  $CO_2$  content of the blood  $[CO_2]_b$ . The  $CO_2$  tension of the blood ( $pCO_2$ ) in millimeters Hg and the bicarbonate concentration of the serum  $[BHCO_3]_s$  in millimols per liter were calculated from the above determinations by use of the Hastings-Shock nomogram.<sup>8</sup> The serum salicylate levels were estimated by the method of Keller.<sup>9</sup> Six-minute samples of expired air were collected in a Tissot spirometer for the estimation of respiratory volume; all air volumes were corrected to 0°C and 760 mm. pressure. Three 1-minute counts of respiratory rate were made during each 6-minute air-collection period. These counts were averaged to represent the respiratory rate per minute for that particular time.

$[BHCO_3]_s$  and  $pCO_2$  are shown in Table 1.

**CLINICAL SYMPTOMATOLOGY.** All but 2 of the subjects developed symptoms of salicylism: tinnitus, nausea, drowsiness, headache, and anorexia. One subject vomited once, an hour and one-half after the last dose of aspirin; another vomited twice, immediately after the last dose of aspirin and again 6 hours later. Most of the symptoms developed after all the aspirin had been given and persisted for about 8 hours. One subject, however, who attained a peak blood salicylate level of 40.2 mg. per 100 cc., continued to complain of tinnitus for 48 hours after the last dose of aspirin. No systematic changes were found in body temperature or in blood pressure levels.

**SERUM SALICYLATE LEVELS.** The administration of 12 gm. of aspirin according to the dosage schedule described above resulted in a rise in the

TABLE 1.—CONTROL DETERMINATIONS.

Subject No.	pHs at 38°C	$V_c$ per cent	$[CO_2]_b$ mM/L	$pCO_2$ mm. Hg.	$[BHCO_3]_s$ mM/L	Resp. Vol. L/Min. Std. Cond.
1	7.38	44	22.9	46.2	26.8	6.67
2	7.36	47	21.3	45.3	25.0	5.35
3	7.41	49	21.7	42.3	26.2	7.48
4	7.34	39	21.5	44.0	24.5	7.3
5	7.42	42	20.4	40.5	25.2	6.6
6	7.38	42	23.2	45.6	26.2	6.2
7	7.35	43	23.5	49.8	26.9	8.8
8	7.39	47	21.9	43.8	24.2	7.4
9	7.37	38	22.2	43.6	25.0	7.0
10	7.36	47	20.1	43.0	23.5	7.9
Mean	7.39	43.8	21.9	44.4	25.4	7.1

**TREATMENT OF DATA.** Results are presented in terms of mean values for the group of 10 subjects. Displacements of respiratory volume,  $pH_s$ ,  $[BHCO_3]_s$  and  $pCO_2$  were calculated for each subject by subtracting the control values for the individual subject from the experimental values. Mean values of the various displacements were then computed and curves plotted.

**Results. CONTROL VALUES.** All values are well within previously established normal limits.<sup>14</sup> The individual and mean control values for respiratory volume in liters per minute,  $pH_s$ ,

serum salicylate level (Fig. 1). An average peak level of 39 mg. per 100 cc. (range 30.1 to 50.3 mg.) was attained 2 hours after the last dose of aspirin. After the peak was reached, the level dropped at a uniform rate for the next 18 hours at which time the average serum level was 30% of the peak concentration.

**RESPIRATORY CHANGES.** The respiratory volume in liters per minute rose to an average maximum increment of 4.0 L./min. 2 to 4 hours after the

peak in the blood salicylate level. The average recovery 14 hours later was only one-half the total displacement (Fig. 1).

No consistent significant changes were found in the respiratory rate per minute.

**ACID-BASE CHANGES.** The changes in the acid-base equilibrium of the blood were an increase in  $pH_s$  which amounted on the average to 0.06, a decrease in  $pCO_2$  of 11 mm. Hg. and a decrease in  $[BHCO_3]_s$  of 2.8 mM/L.

(Fig. 1). The height of displacement in those values occurred 4 hours after the last dose of aspirin. Nineteen hours after the last dose of aspirin the acid-base changes were still displaced from the normal values.

The values of  $pCO_2$ ,  $[BHCO_3]_s$  and  $pH_s$  for each subject were plotted on triaxial coordinates.<sup>15</sup> This method of plotting acid-base changes of the blood makes use of 3 axes; one for  $pH_s$ , one for serum bicarbonate, and the other for  $CO_2$  tension. The units on

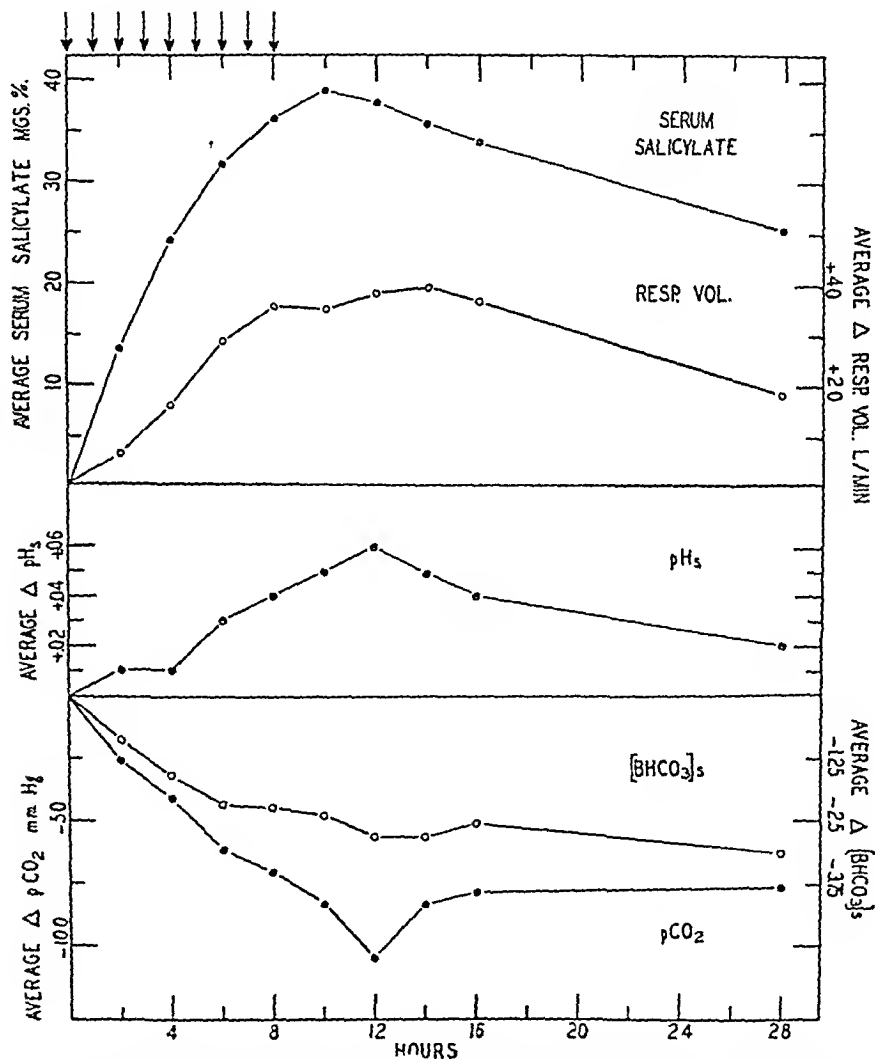


FIG. 1.—Average changes in blood chemical findings and respiratory volume for 10 subjects during and following oral administration of 12 gm. of aspirin. Arrows in upper-left corner indicate aspirin dosage at hourly intervals of 1.3 gm. each, except for the last arrow which represents a dose of 1.6 gm.

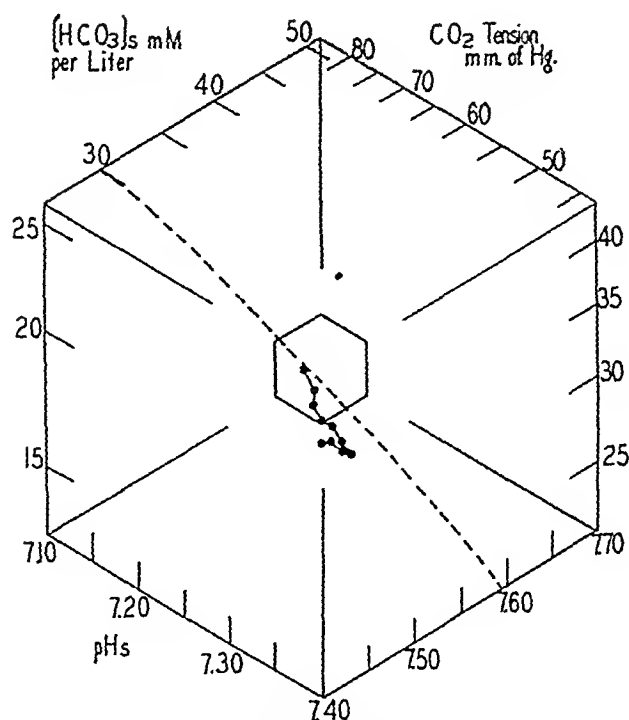


FIG. 2.—Average pathway of displacement and recovery of the acid-base balance of the blood during and following oral administration of aspirin. Each point represents determinations at 2-hour intervals; the last point is the determination at the 28th hour.

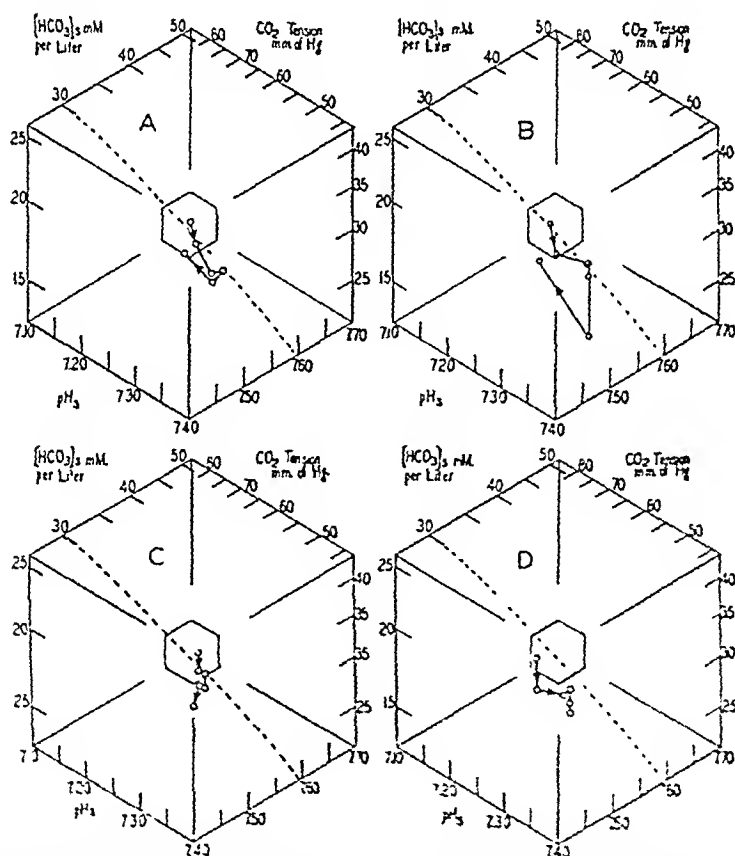


FIG. 3.—Individual pathways of displacement and recovery of acid-base balance of the blood. Each point represents values at 1-hour intervals; the last point shows values at the 28th hour.



these scales are arranged in accordance with the Henderson-Hasselbalch equation so that when any 2 variables are known, the third is determined in the coordinate system. The broken line in Fig. 2 represents the  $\text{CO}_2$  absorption curve of whole blood when titrated with carbonic acid *in vitro*. A comparable titration with  $\text{CO}_2$  occurs in the body by loss of or accumulation of  $\text{CO}_2$  by the lungs. Changes in the acid-base equilibrium of the blood along or parallel to the  $\text{CO}_2$  absorption curve are due to respiratory effects, either  $\text{CO}_2$  excess or  $\text{CO}_2$  deficit. It has been shown experimentally<sup>15</sup> that addition (or loss) of fixed acid (or base) produces changes in the acid-base equilibrium along an axis at right angles to the  $\text{CO}_2$  absorption curve.

Average values for all subjects were calculated for each 2-hour interval for the first 16 hours and again at the 28th hour. A plot of these points shows that the pathway of displacement was along a  $\text{CO}_2$  absorption curve for whole blood (Fig. 2).

The individual pathways of 4 of the subjects at 4-hour intervals are shown in Fig. 3. Of these, "A" (Subject 7) and "B" (Subject 8) followed the average pathway of all the subjects; "C" (Subject 3) showed a constant  $\text{pH}_s$  throughout the course of the experiment; while "D" (Subject 4) followed a pathway of a  $\text{CO}_2$  absorption curve with no signs of recovery during the course of the experiment.

**DISCUSSION. RESPIRATORY CHANGES.** It has long been known that hyperpnea often occurs with salicylism. Guest and co-workers,<sup>7</sup> however, reported no constant hyperpnea in their subjects. This was apparently a clinical observation, since no data for either respiratory volume or rate were given. Their conclusion that salicylates produced primary hyperpnea was based on the observations of lowered  $\text{CO}_2$  tension of

the blood. In animals, Rapoport and Guest<sup>11</sup> found the intravenous or intramuscular administration of methyl and sodium salicylates caused a primary hyperventilation; similar results were reported by Boyle and co-workers.<sup>3</sup> In the present experiments, it was found that although an increase in respiratory volume (hyperpnea) occurred in all the subjects, there was no systematic increase in respiratory rate (tachypnea).

**ACID-BASE CHANGES.** The literature contains numerous and conflicting reports concerning the changes induced by salicylates on the acid-base balance of the blood. The main part of disagreement has been whether salicylates produce a metabolic acidosis or a respiratory alkalosis. The confusion has arisen partly because only  $\text{CO}_2$  content has been determined. Since this single variable is low in both conditions, it is necessary to estimate both the  $\text{pH}$  of the blood as well as the  $\text{CO}_2$  content to determine whether an alkalosis or an acidosis exists. A discussion of the limitations of  $\text{CO}_2$  combining-powers as a criterion of acid-base status is beyond the scope of this paper.

Following the intravenous and intramuscular administration of salicylates in animals<sup>3,11</sup> and the oral administration in children,<sup>7</sup> it was found that a respiratory alkalosis occurred. Ryder and associates<sup>12</sup> report the case of a 16-year-old patient with acute rheumatic fever who developed a respiratory alkalosis after a total of 26 gm. of sodium salicylate had been given by mouth in a 6-day period. It is of interest that Coburn<sup>4</sup> reported no untoward effects from the intravenous administration of 10 to 20 gm. of sodium salicylate in 6 to 8 hours in the treatment of acute rheumatic fever among Navy personnel.

It has been shown that the pathway of decompensation and recovery of

the acid-base equilibrium from over-breathing in normal adults follows the  $\text{CO}_2$  absorption curve of whole blood.<sup>15</sup> The average pathway of displacement of the acid-base equilibrium in the present experiment also follows the  $\text{CO}_2$  absorption curve for whole blood (Fig. 2). The recovery pathway, however, suggests a degree of renal compensation for the primary respiratory alkalosis. Previous experiments have shown that with short periods of marked hyperventilation (5 to 20 minutes) renal compensation does not occur.<sup>15</sup> The differences in results might be attributed to the duration (24 to 28 hours) of the hyperventilation in the experiment reported here.

**GENERAL.** From the preceding it is apparent that therapeutic doses of aspirin in normal human adults can produce a respiratory alkalosis that persists for at least 20 hours after the last dose of aspirin. It is known that hyperthermia *per se* may lead to hyperventilation.<sup>10</sup> Inasmuch as aspirin is commonly used in a variety of conditions, especially those in which fever is present, the total effect of hyperventilation from fever and from aspirin might lead to a severe respiratory alkalosis. It has been a common clinical practice in the past to give alkali to patients with salicylism. Most of the reports deal with children in whom a secondary metabolic acidosis, superimposed on an undoubtedly primary respiratory alkalosis, was present at time of admission to the hospital. These patients responded well to intravenous fluids, glucose, and alkali.<sup>1,5</sup> It has also been shown that the administration of sodium bicarbonate to patients receiving salicylates is followed by a more rapid reduction in the blood salicylate level than occurs otherwise.<sup>16,17</sup> However, the injudicious use of alkalis in patients in whom the pathway of acid-base imbalance is unknown might cause fur-

ther derangement of the acid-base equilibrium in case a respiratory alkalosis were present. To prevent this, blood studies should include both  $\text{CO}_2$  content and pH in order to determine the proper therapy.

**Summary.** Ten normal adults were given hourly doses of 1.3 gm. of aspirin orally for a total of 12 gm. Determinations of respiratory volume, respiratory rate, blood pressure, pulse rate, temperature,  $[\text{BHCO}_3]_s$ ,  $\text{pH}_s$  and  $\text{pCO}_2$  were made at 2-hour intervals for 16 hours and again at the 28th hour. Determinations of serum salicylate levels were made on the same schedule.

The administration of aspirin resulted in a respiratory alkalosis in all subjects; the respiratory volume increased (to an average maximum of 4.0 L./min), the  $\text{CO}_2$  tension of the blood diminished (to an average maximum of 10.5 mm. Hg), the  $\text{pH}_s$  increased (to an average maximum of 0.06) and the  $[\text{BHCO}_3]_s$  decreased (to an average maximum of 3.0 mM/L.).

The maximum displacement of the acid-base equilibrium occurred 2 to 4 hours after the maximum blood salicylate level (average 39 mg. per 100 cc.) was reached. Twenty hours after the last dose of aspirin there was still a significant displacement of all the factors measured.

Symptoms of salicylism occurred in 8 of the 10 subjects.

No significant changes were observed in respiratory rate, pulse rate, temperature or blood pressure.

**Conclusion.** In normal adults the administration of therapeutic doses of aspirin may result in a primary respiratory alkalosis caused by a hyperpnea without an accompanying tachypnea.

The necessity for adequate blood studies in treating a patient with salicylism is discussed.

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# STUDY OF FIXED TISSUE SECTIONS OF STERNAL BONE MARROW OBTAINED BY NEEDLE ASPIRATION

## III. METASTATIC CARCINOMA IN STERNAL BONE MARROW

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THE diagnosis of metastatic carcinoma can occasionally be made by finding tumor cells in films of the sternal bone marrow obtained by needle aspiration. Rohr and Hegglin<sup>1</sup> found metastatic tumor cells in the sternal marrow in 10 of 74 cases and Stoger<sup>2</sup> in 8 of 110 cases of carcinomatosis. However, many bizarre, atypical, and distorted cells are frequently seen in films of the sternal marrow and these may occasionally be mistaken for tumor cells. The diagnosis of metastatic carcinoma on this basis may therefore be open to question. A more accurate diagnosis can be made by finding nests of cancer cells in histologic sections made from sternal marrow particles by techniques previously described.<sup>3,4</sup> This report describes a study of histologic sections of sternal marrow obtained by aspiration biopsy from patients with malignant tumors.

**Material and Methods.** Aspiration biopsy of the sternal marrow was performed on 49 patients with known malignant tumors and on one patient in whom the diagnosis of carcinoma was suspected but not proven prior to sternal aspiration. Of the 49 patients with known malignancy, 29 had clinical evidence of widespread metastases and 20 had no known metastases except for involvement of regional lymph nodes. The group included patients with carcinoma of the breast, lung, kidney, prostate, gastrointestinal tract, nasopharynx, cervix, testicle, bone, and skin (Table 1). There were 5 patients in whom the primary site was unknown.

Sternal puncture was performed by the

usual technique, the needle being inserted between the 2d and 3d ribs, and the material obtained was prepared by methods previously described.<sup>4</sup> Films were made from the first drop of marrow obtained and 1 cc. of marrow content was then aspirated. The small marrow particles were separated from the blood and suspended in plasma. The particles were then allowed to collect by sedimentation or flotation for 30 minutes in an ice box at 4° C. and the excess plasma removed. One drop of 0.25 molar calcium chloride was then added to clot the suspension of marrow particles and plasma. The resultant clot was fixed in Zenker's acetic acid fixative and prepared and sectioned by routine histologic technique. Better sections are obtained if the particles of marrow are pushed to one side with a sharp, pointed probe immediately after the calcium chloride has been added, after which all the plasma possible is aspirated with a capillary pipette. This removes an excess of plasma so that the sections contain more marrow particles relative to the amount of plasma present.

**Results.** Of the 50 patients, 7 were found by this technique to have metastatic carcinoma in the sternal bone marrow (Table 1). Tumor cells were found in the marrow films in 4 of these 7 patients. There were no instances in which tumor cells were observed in the film when they could not be found in histologic sections.

Metastatic carcinoma was found in the marrow of one patient in whom all clinical and laboratory findings, including extensive roentgenographic examinations, were negative (Fig. 3), and in whom sternal marrow aspiration

was performed because the history and course were suggestive of carcinoma. The marrow findings comprised the only objective evidence of carcinoma which could be demonstrated antemortem. Postmortem examination revealed an adenocarcinoma of the kidney, metastatic to the pleura, liver, and bone marrow.

Two cases of carcinoma metastatic to the sternal marrow were found in

patients who were thought to have only regional metastases and were therefore subjected to operation. Both of these patients subsequently developed roentgenographic evidence of widespread bony metastases and have since died. The diagnoses were confirmed on postmortem examination.

Metastatic carcinoma was found in the sternal marrow in 2 of 10 patients with carcinoma of the breast; in 2 of 8

TABLE 1.—SUMMARY OF MATERIAL

Primary Site of Carcinoma	Number of Cases	Metastatic Lesions Found in Sternal Marrow
Breast*	10	2
Lung	8	2
Kidney	4	2
Prostate	5	1
Gastrointestinal Tract	10	0
Nasopharynx	3	0
Uterine Cervix	2	0
Testicle	1	0
Bone (Ewing's Endothelioma)	1	0
Skin (Melanosarcoma)	1	0
Primary Site Unknown	5	0
Total	50	7

\*Including one Male

TABLE 2.—DISTRIBUTION AND INCIDENCE OF METASTASES.

Type of Case	Number of Cases	Metastases in Sternal Marrow
Not Known to be Metastatic*	20	2
Known to be Metastatic:		
Metastatic to Bone	12	4
Not Metastatic to Bone	17	0
Undiagnosed Prior to Sternal Biopsy	1	1
Totals	50	7

\*Includes Regional Lymphnode Involvement

TABLE 3.—CORRELATION OF DEGREE OF ANEMIA WITH ACTIVITY OF MARROW

Activity of Marrow Estimated from Histologic Sections	Number	Degree of Anemia*		
		None	Moderate	Severe
Normal	35	16	17	2
Hypoplastic	9	2	6	1
Markedly Hypoplastic	6	0	2	4
Totals	50	18	25	7

\*Moderate anemia

Red blood count 3.0 million to 4.0 million per c. mm.  
Hemoglobin between 9.0 and 12.0 gm. per 100 ml.

Severe anemia

Red blood count less than 3.0 million per c. mm.  
Hemoglobin less than 9.0 gm. per 100 ml

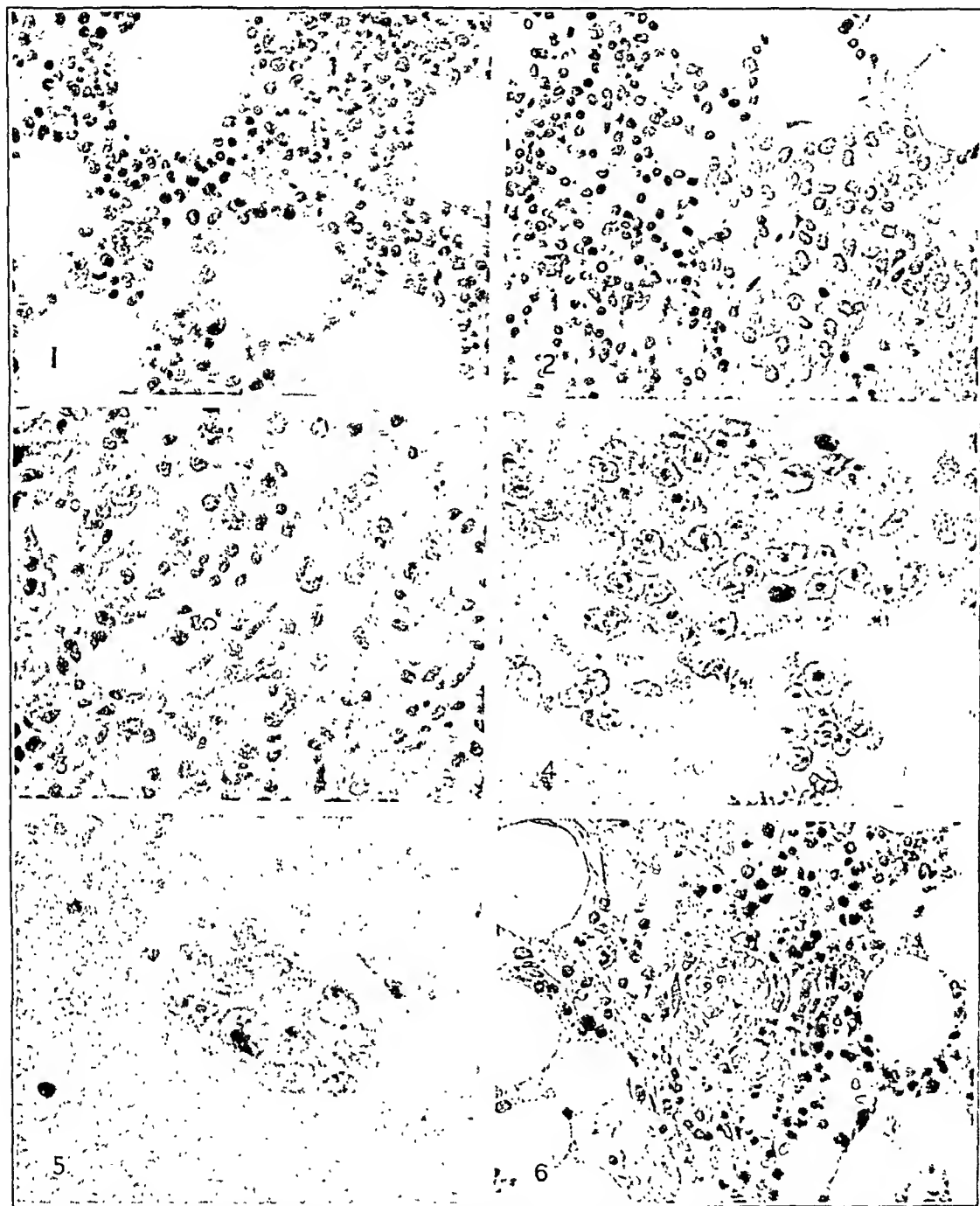


FIG. 1.—Normal marrow (450 x). FIG. 2.—Carcinoma of the breast metastatic to the sternal marrow (450 x). FIG. 3.—Carcinoma of the kidney metastatic to the sternal marrow. Note acini (550 x). FIG. 4.—Carcinoma of the prostate metastatic to sternal marrow (550 x). FIG. 5.—Carcinoma of the breast metastatic to sternal marrow (970 x). FIG. 6.—Granulomatous lesions in sternal bone marrow (550 x).

patients with carcinoma of the lung; in 2 of 4 patients with carcinoma of the kidney, and in 1 of 5 patients with carcinoma of the prostate (Table 1). Only 4 of 12 patients with roentgenographic evidence of metastases to bone were found to have metastatic carcinoma in the sternal marrow (Table 2).

Tumor cells can readily be recognized in sections of the sternal marrow. Occasionally, however, a circumscribed granulomatous lesion may be mistaken for carcinoma (Fig. 6). The tumor cells occur as a syncytium which can be clearly differentiated from loosely arranged cells of the normal

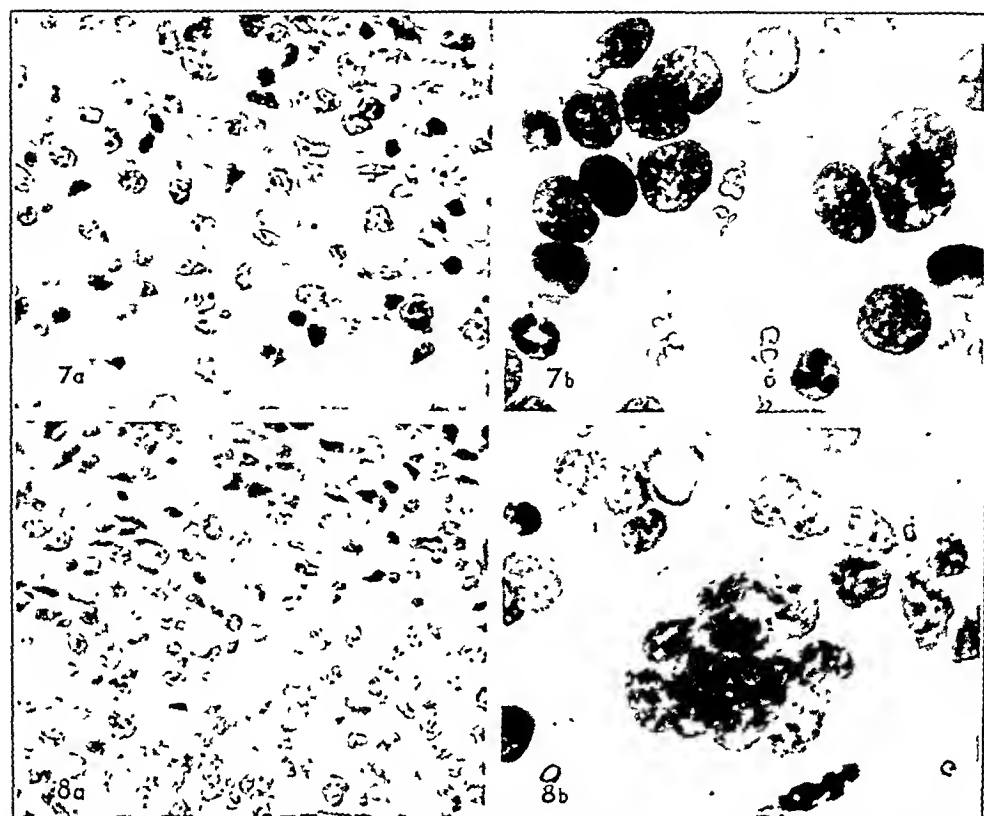


FIG. 7 A.—Renal carcinoma metastatic to sternal marrow (550 x). FIG. 7 B.—Metastatic tumor cells in marrow film. Same patient as FIG. 7 A. Wright stain (970 x). FIG. 8 A.—Carcinoma of the bronchus metastatic to sternal marrow (550 x). FIG. 8 B.—Tumor cells in marrow film. Same patient as in FIG. 8 A. Wright stain (970 x).

TABLE 4.—ANEMIA IN PATIENTS WITH CLINICAL EVIDENCE OF METASTASES

Degree of Anemia	Number	Activity of Marrow		
		Normal	Hypoplastic	Markedly Hypoplastic
None	10	8	2	0
Moderate	11	10	3	1
Severe	5	2	1	2
Totals	29	20	6	3

TABLE 5.—ANEMIA IN PATIENTS WITH METASTASES TO THE BONE

	Number	Degree of Anemia			Histologic Activity		
		None	Moderate	Severe	Normal	Hypoplastic	Hypoplastic
X-Ray Evidence of Metastases to Bone	8	3	5	0	6	2	0
Metastases Found in Histologic Section	7	1	1	5	1	2	1

marrow. They may replace the marrow entirely (Figs. 7A and 8A) or may appear as isolated nodules surrounded by relatively normal or hypoplastic marrow (Fig. 2). The tumor cells are usually large, with vesiculated nuclei and scanty cytoplasm. They tend to be basophilic when stained with hematoxylin and eosin, and mitotic figures are common. In most cases there is a marked tendency toward anaplasia. The diagnosis of metastatic carcinoma was not made on the basis of scattered abnormal cells, although occasionally isolated cells of abnormal appearance were present and were highly suggestive of carcinoma.

Tumor cells in the bone marrow films appeared as large, bizarre cells, usually in groups or clumps, with ill-defined, faint blue cytoplasm, when stained with Wright's stain (Figs. 7B and 8B). The cytoplasm was frequently entirely absent. The nucleus usually appeared to be densely hyperchromatic and reticulated. One to 3 "robin-egg blue" nucleoli were usually visible. Basket cells were common. Occasionally the cells appeared to be in the process of division. When such cells are present in large numbers, a diagnosis made from the Wright stained film is probably reliable. The occurrence of large numbers of such cells is uncommon, however.

Differential counts of the cells in the bone marrow films revealed no characteristic pattern. Occasionally the granulocytic/erythroid rate was high, especially in hypoplastic marrows. Plasma cells were found in a higher percentage than usual in a few patients with advanced carcinomatosis, but this is not a consistent or characteristic finding.

A marked increase in plasma cells was noticeable in the histologic sections in 5 cases (3 carcinomas of the lung, 1 of the breast, and 1 of the kidney). Metastases were likely in these pa-

tients, from a clinical standpoint, but they were not found in the sections. Hemosiderin deposits were noticeably increased in 2 of these cases. These 2 patients were severely anemic. The occurrence of hemosiderin deposits suggests an inability to utilize iron in hematopoiesis, as occurs in certain anemias associated with infection. Solitary lymph follicles were present in 6 cases.

The occurrence of anemia and its correlation with the activity of the bone marrow as estimated from histologic sections was investigated. In the entire group of 50 patients, 18 had no anemia, 25 had moderate anemia (red blood count 3 to 4 million per cu. mm., hemoglobin 9 to 12 gm.), and 7 had severe anemia (red blood count less than 3 million per cu. mm., hemoglobin less than 9 gm.). A normally active bone marrow was present in 35 patients, a hypoplastic marrow in 9 patients, and a markedly hypoplastic marrow in 6 patients (Table 3).

Of the 29 patients in whom metastases were evident clinically, 10 had no anemia, 14 had a moderate anemia, and 5 had a severe anemia. Twenty of these patients had a normally active bone marrow, 6 a hypoplastic marrow, and 3 a markedly hypoplastic marrow (Table 4).

Five of the 7 patients in whom metastases were found in the bone marrow had a severe anemia, 1 had a moderate anemia, and 1 had no anemia. In 4 of the 5 patients with severe anemia, the bone marrow samples studied showed almost complete replacement of normal elements with tumor, and 1 had a hypoplastic marrow. The patient without anemia had a hypoplastic marrow and the patient with moderate anemia had a normal marrow (Table 5).

In 8 patients with roentgenographic evidence of bony metastases, but in whom tumor cells were not found in the marrow sections, 5 had a moderate



anemia and 3 had no anemia. Six of these patients had a normal marrow and 2 a hypoplastic marrow (Table 5).

**Discussion.** The incidence of metastasis to the sternal marrow which occurred in this series is probably considerably higher than the incidence of metastasis in all patients with carcinoma. Many of the patients were deliberately selected in whom metastatic lesions were demonstrable, especially to bone. If more patients with early carcinoma or with carcinomas that do not commonly metastasize to bone had been studied, it is likely that the incidence of metastasis to marrow would have been much lower.

Metastatic lesions were found only in patients with carcinoma of the breast, lung, kidney, and prostate, all of which commonly metastasize to bone. The ability to demonstrate metastatic lesions in 2 patients who underwent operation when other evidence of metastases was lacking, and the absence of any other objective evidence of cancer in another patient, suggests usefulness of the method. It was occasionally impossible to obtain marrow from patients with known metastatic lesions to the bone. This was especially true of patients with carcinoma of the prostate and was attributed to sclerotic or fibrotic changes in the marrow, which prevented aspiration through the needle.

It is obvious, of course, that a negative finding does not preclude the possibility of a metastatic lesion in the marrow. In view of the lack of uniformity of the bone marrow the entire tissue block should be sectioned serially and representative portions studied for metastatic lesions.

Interpretation of the anemia in these patients is difficult. The degree and type of anemia in patients with carci-

noma may be affected by loss of blood and inadequate food intake, in addition to which other unknown factors may contribute to failure of proper hematopoiesis. Anemia was present in most, but not all, cases when metastatic tumor was found in the histologic sections. Normal blood values and a normally active marrow occurred not infrequently in patients with roentgenographic evidence of bony metastases and the same was true of patients with metastases in sites other than bone. Inspection of the data reveals that in many instances there was no correlation between the degree of anemia present and the activity of the marrow, as demonstrated by study of the aspirated particles.

**Summary and Conclusions.** Of 50 patients with malignant tumors, 7 were found to have metastatic lesions in the sternal bone marrow as demonstrated in tissue sections of particles obtained by needle biopsy. This does not represent a true incidence, however, the over-all percentage for all types of carcinoma probably being much lower. Sternal marrow metastases were found only in the case of those tumors which have a tendency to metastasize to bone. Metastatic lesions were found in the marrow in 2 patients after operations for carcinoma of the breast and lung, respectively. In 1 patient a metastatic lesion in the marrow was the only positive antemortem evidence of carcinoma. This would indicate that the procedure might be of benefit preoperatively in cases of carcinoma which are likely to metastasize to bone, and as a diagnostic tool in selected cases. Anemia was not a consistent finding and no correlation could be drawn between the occurrence of anemia and the activity of the bone marrow.

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# THE BLOOD PICTURE IN LEPROSY

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A FEW papers on the blood picture of leprosy have already been published. No general or definite agreement, however, has ever been reached, and different workers give conflicting results.

It must be emphasized that we do not by any means regard the blood picture as being of such paramount importance that, for instance, it would necessarily aid in the diagnosis or prognosis of the disease. At any rate, the problem is still unsolved. Certain changes, however, do occur, and the interpretation of such changes should interest the leprologist and the hematologist alike. What is more, we feel that since all our patients are Chinese our results may be regarded as an independent contribution for comparison with those obtained from patients of other nations.

It is not proposed to review the literature exhaustively. Some of the more important papers must be mentioned. The most complete is apparently that of Cerri (1942),<sup>2</sup> who studied in Italy the blood and bone-marrow of 35 lepers. A list of 47 references was given. Of the blood, estimations were made of the hemoglobin, the number of red and white cells and the differential white cell counts. Leukopenia of 2,600 and 4,150 respectively was found in 2 cases, leukocytosis up to 14,850 was found in 5, anemia was a constant feature, nearly always hypochromic, with some degree of anisocytosis, and rarely poikilocytosis; neutral metamyelocytes were also present but not in

large numbers, non-segmented neutrophils were more common, up to 35% of the neutrophils.

Arisumi (1931)<sup>1</sup> working in Formosa, found that the red corpuscles were reduced in number and a fairly high proportion of basophil-punctate and polychromatophil cells were seen, together with anisocytosis and poikilocytosis, but no nucleated form. The leukocytes were always increased in number, especially in advanced nodular cases, with some decrease in lymphocytes. The eosinophils were few, but might become increased. The hemoglobin was decreased in proportion to the activity of the disease, and the hemoglobin index was low.

In 31 cases in Sardinia, Pinetti (1931)<sup>3</sup> found a slight anemia, a very variable Arneth count, often shifted to the right, and seldom observed eosinophilia.

Some attempts have been made to associate the blood findings with the progress and prognosis of the disease. Thus, Peschkowsky (1934)<sup>7</sup> observed that monocytosis was an unfavourable sign as it was associated with the formation of fresh granulomata with proliferative chronic inflammation. On the other hand, lymphocytosis was favourable in most cases, as it coincided with a period of convalescence and decrease of the inflammatory process. Polymorphonuclear leukocytosis accompanied exacerbations of the disease with suppurative inflammation and subsequent destruction of the bacilli in the polymorphonuclear neutrophils. Fonte

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(1941)<sup>4</sup> reported that exacerbations of the disease, acute or subacute, were preceded by leukocytosis, mainly of the polymorphonuclear elements; regressions of the lesions by reduction of these and increase of large mononuclears; in convalescence, both were reduced with corresponding increase of small lymphocytes.

The reason for considering these findings will be appreciated when they are compared with our results.

**Present Study.** Attached to the West China University Hospital, Chengtu, is a leprosarium, superintended by Dr. W. Crawford, with a normal capacity of 45 beds. During the period between November, 1945, and June, 1947, the blood picture of 36 lepers was examined.

The work was interrupted for some time by the departure of the senior author (S.K.). Later, beginning from October, 1946, when promin treatment was initiated, it was found necessary to check periodically the blood picture of those who received treatment, and so this work was further substantiated and completed. In the earlier period, we personally did several determinations of the red blood cells, hemoglobin, white blood cells and differential white cells, of each of the 19 patients then in the leprosarium. After the first few rounds, we wanted to find out if any of the patients had other parasitic infestations. As no parasites were encountered in the blood smears, the stools of all were examined, and treatment for ascaris and hookworm, the 2 principal findings, were given where indicated. More counts were made after treatment and a second examination of the stools, which were then all negative. The second part was entirely carried out by the technicians in the Hematology Department of the Hospital, directed by Dr. Y. T. Beh. Two complete hemograms of each of the 27 patients were done. Among

these 27, 10 were in our first batch of 19, so the total number of patients examined was 36.

It should be stated that these patients had received various forms of treatment for leprosy, chaulmoogra oil, moolgrol, diphtheria toxoid, alepol and promin. Whether these drugs have any effects on the blood pictures or not must therefore be considered. Generally speaking, we think that they have none, for two reasons. First, the pharmacological actions of these drugs have not been known to cause any actions in the peripheral blood elements. The case of promin is somewhat different. It is stated that the most frequent toxic manifestation of promin is a slow destruction of the erythrocytes; also, a small number of patients may develop leukopenia. Cases 1 to 27 were those who received promin. Hemograms were done for everyone of them before treatment was started, and repeated about 3 months later. From the results of the 2 hemograms little change, however, was observed in both the red and white cells counts. The relative leukopenia of Cases 15 and 20 (see Table 2) was present at the beginning and was unaffected by promin. Therefore, we think that promin, like the other drugs, did not have any noticeable effect on our results. Also, when the first part of this work was being done none of the patients had been receiving any specific treatment, which was stopped for some time because there was a universal lack of supply of drugs. A second thought would be to associate some of the changes with the 2 generally accepted types of leprosy, the neural and the hypomatous. A complete physical survey of the patients was done, and they were separated into these 2 divisions. We might also say that none of these patients had any intercurrent diseases, as each of them had been thoroughly checked before admission, and each

of them was proved to have leprosy by biopsy. While doing the hemograms, the Kahn tests of all but 2 of the 27 patients were found to be positive. It should be remembered, however, that it has been generally accepted that leprosy as well as syphilis gives a positive Kahn test. (Rogers and Muir, 1946,<sup>9</sup> and Strong, 1943.<sup>10</sup>)

**Results.** The results of our studies are given in Tables 1 and 2. For the morphological studies of the red cells and the differential white counts, Wright's stain was used throughout,

and the Wintrobe hematocrit was used for all hematocrit determinations of the red cells.

As stated above, for Cases 1 to 27, two complete hemograms were done at different periods, and for our original 19 cases, all the counts were repeated for not less than 5 times. Two-hundred white cells were counted in the differential white counts. All figures given in the tables represent the mean values.

The standard figures which we have adopted as 'normal' are those given by Wintrobe (1946).<sup>12</sup> Wu and Tsai

TABLE 1. RED BLOOD CELL DETERMINATIONS IN 36 CHINESE LEPERS

Case No.	R.B.C. Total Count mlls. per c.mm.	Hgb. gm. per 100 cc.	Vol. Packed R.B.C. cc. per 100 cc.	Mean Corpuscular Volume (c.μ.)	Mean Corpuscular Hgb. (γγ)	Mean Corpuscular Hgb. Conc. %	Reticulo-cytes per cent	Sedimentation Rate mm.	Change in Sedimentation Rate	Type of Anemia
Normal Values	5.4 ± 0.8	16 ± 2	37 ± 7	87 ± 5	29 ± 2	33 ± 2	0.5-1.5	0-10		
1	4.15	12.0	44	97	24	29	0.1	19	increased	macrocytic hypochromic
2	5.01	14.2	43	86	24	32	0.1	10	increased	—
3	5.91	11.3	45	84	21	25	0.1	0	—	normocytic hypochromic
4	4.12	10.1	35	85	25	29	0.1	20	increased	normocytic hypochromic
5	4.50	9.7	37	80	21	26	0.1	12	increased	microcytic hypochromic
6	3.04	8.4	32	89	23	26	0.1	8	—	normocytic hypochromic
7	4.04	13.3	37	80	28	35	0.1	28	increased	—
8	4.05	12.7	41	89	25	31	0.4	29	increased	normocytic hypochromic
9	3.69	10.0	41	110	27	24	0.1	3	—	macrocytic hypochromic
10	4.05	11.9	42	91	26	29	0.1	32	increased	normocytic hypochromic
11	3.94	11.0	40	102	28	27	0.3	19	increased	macrocytic hypochromic
12	4.24	11.6	35	85	20	30	0.1	5	—	normocytic hypochromic
13	4.18	10.1	38	92	25	26	0.3	20	increased	normocytic hypochromic
14	4.83	10.4	41	85	29	27	0.1	32	increased	normocytic hypochromic
15	3.55	9.8	32	91	28	31	0.2	21	increased	—
16	5.34	11.6	41	77	21	28	0.1	18	increased	microcytic hypochromic
17	3.45	9.2	37	102	26	25	0.5	20	increased	macrocytic hypochromic
18	4.50	12.1	49	110	27	24	0.1	25	increased	macrocytic hypochromic
19	4.27	10.2	36	89	25	29	0.9	22	increased	normocytic hypochromic
20	4.62	13.3	44	94	28	30	0.1	12	increased	—
21	4.01	10.4	34	85	25	30	0.1	26	increased	normocytic hypochromic
22	3.42	6.6	30	88	19	22	0.1	12	increased	normocytic hypochromic
23	4.60	12.7	43	93	27	29	0.1	24	increased	normocytic hypochromic
24	5.19	12.1	49	97	23	24	0.1	23	increased	macrocytic hypochromic
25	4.02	10.3	41	102	25	24	0.1	44	increased	macrocytic hypochromic
26	3.20	8.7	24	75	27	36	0.1	23	increased	microcytic
27	3.68	10.1	30	83	27	33	0.1	23	increased	—
28	3.62	10.6								
29	4.48	11.6								
30	3.53	10.9								
31	5.05	11.9								
32	3.21	12.1								
33	3.61	10.4								
34	4.23	10.1								
35	3.80	8.7								
36	3.52	8.1								
.....Not Done.....										
Average	4.20	10.7	38	90	24	29	0.17	19		
Standard Deviation	-1.2	-3.3	-9	+3	-5	-5	?	+9		

TABLE 2. WHITE BLOOD CELL DETERMINATIONS IN 36 CHINESE LEPROS

Case No.	Sex	Age	Differential Count per cent								Summary of Results					
			1-3		25-33		3-7		0-75		leukopenia <5,000	shift to left	shift to right	eosinophilia >3	lymphocytosis >33	monocytosis >7
			1-3	25-33	3-7	0-75	>10,000									
Normal 5	103	5	51	62	4-6	1-2	1-2	1-2	1-2							
1	10	4	12	41	3	33	11	-	-	+	+					+
2	11	0	7	50	3	37	3	-	-	+	+			+		
3	8	8	8	55	3	27	7	-	-		+					
4	9	5	9	47	2	37	5	-	-		+			+		
5	7	0	8	18	4	51	18	1	1		+	+		+		+
6	13	6	14	21	13	42	9	1	1	+	+			+		+
7	5	0	10	22	2	54	11	1	1		+			+		+
8	9	1	12	35	21	22	10	-	-		+	+				+
9	10	0	18	36	3	35	7	1	1		+			+		
10	5	3	14	35	1	39	11	-	-		+			+		+
11	9	2	6	44	1	42	4	-	-		+	+		+		
12	6	5	12	29	3	50	6	-	-		+			+		
13	7	9	15	44	10	29	2	-	-		+					
14	12	0	13	33	-	45	9	-	-	+	+			+		+
15	5	0	19	20	3	49	9	-	-		+			+		+
16	12	5	10	19	8	31	2	-	-	+	+					+

17	9.7	5	42	--	50	3	—			+		+		
18	5.9	7	48	3	37	5	—		+			+		
19	8.4	4	22	1	63	10	—			+		+		
20	4.5	21	47	--	20	3	—	+						
21	6.0	10	41	1	48	--	—		+			+		
22	9.0	17	43	11	17	11	1		+		+	+		
23	5.0	14	46	1	34	5	—		+			+		
24	7.0	2	57	2	28	11	—			+		+		
25	10.3	19	34	13	31	3	—	+						
26	7.0	11	53	1	20	15	—		+			+		
27	7.4	28	38	1	26	7	—		+					
28	8.2	--	45	4	25	25	1			+		+		
29	8.0	2	22	1	50	25	—			+		+		
30	9.0	--	19	10	34	36	1			+		+		
31	12.6	1	62	1	26	9	1	+				+		
32	7.4	2	50	3	33	12	—			+		+		
33	12.3	3	69	13	12	3	—		+					
34	9.5	2	58	0	25	5	1			+				
35	15.2	1	51	17	18	13	—	+				+		
36	28.8	1	32	2	57	8	—	+			+	+		
Average	8.8	9	10	5	36	10	0.25	10 (28%)	2 (5.5%)	24 (66.7%)	12 (33.3%)	13 (36.1%)	19 (52.2%)	19 (52.2%)

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# EFFECT OF HESPERIDIN METHYL CHALCONE (VITAMIN P) ON DIABETIC RETINOPATHY

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UNDER proper dietary management and with the aid of Insulin therapy, most diabetic patients can be kept in a reasonably normal state of nutrition and in satisfactory metabolic balance as far as gross glycosuria and freedom from frank symptoms of diabetes are concerned. Nevertheless, these clinical criteria of control of the disease have proved inadequate to protect the diabetic against the onset of vascular disease if he lives long enough. This fact has recently been emphasized by Dolger<sup>3</sup> who showed that in a group of 200 patients whose diabetes was observed within a period of 25 years' duration, there was evidence of vascular disease in every case. He concluded that "present day treatment of diabetes has failed to avert the accelerated vascular damage which is an associated phenomenon and not a complication". That this finding may not be invariable is indicated by 2 cases in the Indianapolis series (D.D. and K.R.), whose juvenile diabetes has extended well over 20 years, and who show no demonstrable retinal, renal, or other vascular damage whatsoever. How to prevent or retard vascular degeneration is a problem and a challenge.

The most common and in many cases the earliest manifestation of vascular involvement is the appearance of hemorrhages and exudates in the retina. There have been no satisfactory methods of treatment of these retinal le-

sions, and consequently a therapeutic measure which offers any hope is worthy of consideration. If the progressive course of diabetic retinopathy could be arrested, similar damage to the vascular system in other parts of the body might likewise be favorably influenced.

The early investigations by Szent-Gyorgyi<sup>1</sup> on vitamin C led him to believe that a substance other than ascorbic acid was responsible for the petechial hemorrhages which appear in deficiency states. He identified the substance as a mixture of the flavone glucosides of hesperidin and eriodictyol. There was evidence that the absence of this substance increased capillary permeability and so it was called vitamin P. The vitamin P used in the present study was hesperidin methyl chalcone (H.M.C.); it is derived from the rinds of citrus fruits. (Rutin, another of the flavone glucosides, also has vitamin P activity, differing from hesperidin methyl chalcone in that its potency, according to Scarborough,<sup>3</sup> is about one-half that of pure hesperidin.)

Vitamin P has been suggested as a means of control of the hemorrhagic manifestations of certain disorders.<sup>5,9,10,12,14</sup> The present study was undertaken to determine the effect of vitamin P on the retinal hemorrhages of diabetes. As a part of the investigation additional information was sought in the hope of throwing some light on other factors which might be associated

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with the appearance of retinal hemorrhages. It is well known that diabetic retinopathy tends to be progressive. There is a wide variation in the rate at which fresh hemorrhages and exudates appear, and these lesions may undergo spontaneous absorption for no apparent reason. It is difficult, therefore, to evaluate fully any therapeutic agent unless a large series of cases are followed for a long period. The number of patients so followed in our series is too small to be of statistical significance, but some information has been obtained by a careful study of individual cases.

Twenty-two diabetic patients with retinal hemorrhages have been treated with hesperidin methyl chalcone. The daily dose was small in the beginning but was gradually increased when it became apparent from studies of the effects of administration of massive doses by Kirtley and Peck<sup>8</sup> that there were no side reactions from the drug. All but one of the patients ultimately received between 100 and 300 mg. of the drug daily, and in some instances these doses were exceeded considerably for short intervals.

Systematic examinations of the fundus oculi were made through a dilated pupil by the same examiner (M.M.)

extravasation of plasma from vessels, they may also be a manifestation of increased capillary permeability. On the basis of ophthalmoscopic findings the retinal lesions were arbitrarily divided into 2 groups, early and moderate. Those patients with punctate hemorrhages which did not exceed 5 in number, with or without small waxy exudates, were classified as having early diabetic retinopathy. Where punctate hemorrhages were more numerous and larger deep hemorrhages were present, the retinopathy was classified as moderate. Many of the patients in the latter group showed extensive areas of retinal exudation and a few had cotton wool patches.

**BLOOD PROTEINS.** Schneider, Lewis, and McCullough<sup>15,16</sup> determined plasma protein levels in diabetics by electrophoretic methods and found that the albumin level was usually low in untreated or poorly controlled cases. Total proteins approached normal since there was an increase in the globulin. Adequate treatment and high protein diet restored the albumin to normal levels and in some instances this was accompanied by an improvement in the retinal lesions. Our studies, however, do not indicate any significant alteration in plasma proteins as determined by the modified biuret method

TABLE 1.—BLOOD PROTEINS IN 23 CASES.

Appearance of retina	Number of cases	Albumin (Average)	Globulin (Average)	Total Proteins (Average)
Normal	3	1.65	2.81	7.51
Early Retinopathy	13	1.79	2.90	7.69
Moderate Retinopathy	7	1.60	3.07	7.67

every 2 to 3 months during the period of observation. Each case was followed for an average time of 15½ months, the shortest period being 4 months and the longest 32 months. Every patient showed one or more of the typical types of retinal hemorrhages seen in diabetes. Particular attention was given to the hemorrhagic lesions, since capillary damage may be responsible for their appearance. If the exudates seen in diabetic retinopathy represent the

of Kingsley.<sup>7</sup> A summary of the average protein levels of 23 diabetics is given in Table 1. Individual values were within normal range in 3 patients without retinopathy, 13 with early retinal lesions, and 7 with more advanced hemorrhages and exudates. Protein intake was not less than 1 gm. per kg. of body weight and did not exceed 100 gm. daily. All but 3 patients were regarded as being under satisfactory diabetic control.

**PROTHROMBIN TIME.** Since diabetic retinopathy is characterized by the presence of hemorrhages, prothrombin determinations were made in 33 cases, using the method of Quick. A summary of the results appears in Table 2. Three out of 4 control cases with normal fundi had normal prothrombin times. An increase in prothrombin time was found in 6 of 15 patients with early diabetic retinopathy and 11 of 12 patients with moderate retinopathy. This finding is not in agreement with that of MacLean and Brambel,<sup>11</sup> who reported a decreased prothrombin time in their series of cases treated with dicumarol and rutin. There was no correlation between increased capillary fragility and increased prothrombin time (Table 2). Whether there is any direct relationship between changes in prothrombin time and diabetic retinopathy awaits further study.

**CAPILLARY PERMEABILITY.** Capillary permeability was measured by positive pressure using a blood pressure cuff inflated to diastolic pressure and maintained at that level for 3 minutes. The number of petechiae appearing in the antecubital fossa within an area 1 inch in diameter were counted. Capillary permeability was considered to be increased if more than 20 petechiae were present. Our findings confirm the re-

after a coughing paroxysm. They produced a positive seotoma and the patient sought advice as soon as possible. Some hemorrhages absorbed while others extended into the vitreous where they became organized into bands of retinitis proliferans. In the right eye the retina was detached by the contraction of one of these bands. The appearance of hemorrhages and the course they took was not influenced by taking hesperidin methyl chalcone for a period of 32 months. (This patient also received massive doses<sup>8</sup> up to 15 gm. daily without apparent improvement.)

In 5 patients (Cases 7 to 11) the retinal lesions remained stationary. No fresh hemorrhages or exudates appeared, and those that were present showed no evidence of absorption. The administration of hesperidin methyl chalcone may have prevented any new lesions from developing; or such cases may represent the group of diabetic patients whose retinopathy remains unchanged for long periods.

Five patients (Cases 12 to 16) showed improvement. Hemorrhages absorbed and in Cases 13 and 15 cotton wool exudates disappeared. In Case 12 the patient was used as a control after the hemorrhages absorbed. Hesperidin methyl chalcone was discontinued and

TABLE 2.—PROTHROMBIN TIME AND CAPILLARY FRAGILITY.

Appearance of Retina	Number of Cases	Prothrombin Time		Capillary Fragility		Duration of Diabetes (Yrs.)
		Normal	Increased	Normal	Increased	
Normal	4	3	1	3	1	6½
Early Retinopathy	15	9	6	6	9	7½
Moderate Retinopathy	13	1	12	7	6	10

ports of others that diabetics with retinal changes show increased capillary fragility in most cases.

**Results.** Findings are tabulated in Table 3. Six patients (Cases 1 to 6) showed a definite increase in retinal hemorrhages while undergoing treatment with hesperidin methyl chalcone. Case 5 was an employee of the hospital who was examined at frequent intervals. She developed pre-retinal hemorrhages which would often appear

fresh hemorrhages reappeared in 7 months. Hesperidin methyl chalcone was administered again and the hemorrhages reabsorbed. Unless there was an unusual coincidence of events, it would seem that the medication played some part in the improvement of the retinal lesions. The effect which hesperidin methyl chalcone had on the retinopathy of other patients in this group cannot be definitely established since spontaneous absorption of hem-

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TABLE 3.—SUMMARY OF CASES.

Case No.	Name	Age and Sex	Duration of Diabetes (years)	Blood Pressure	Capillary Fragility		Control & Total Insulin	Retinopathy	Daily Dose of H M C and Months of Treatment	Months H M C Treatment Administered	Results
					N	N					
1	D.G.	66 F	1	110/50			Good 15 U	Early	15 mg. - 3 mos. 75 mg. - 4 mos. 100 mg. - 1 mo. 150 mg. - 1 mo 200 mg. - 8 mos.	17	Hemorrhages increased and cotton wool exudates appeared
2	F. I.	52 F.	1	150/90	100	0	Fair 80 U	Moderate	15 mg. - 11 mos. 100 mg. - 2 mos. 200 mg. - 8 mos. 300 mg. - 5 mos.	21	More hemorrhages appeared while receiving 200 mg. daily
3	A.W.	56 F.	2	130/80	150	0	Good 22 U	Early	15 mg. - 4 mos.	17	More punctate hemorrhages appeared in right eye
4	C.W.	54 F	1	150/70	20	20	Good 0	Early	15 mg. - 3 mos. 60 mg. - 8 mos. 75 mg. - 12 mos	32	Punctate hemorrhages increased in both eyes
5	F.C.	51 F.	20	130/80	100	18	Good 25 U	Moderate	150 mg. - 3 mos. 300 mg. - 6 mos.		Pre-retinal hemorrhages appeared. Some absorbed while others extended into vitreous, forming bands of retinitis proliferans
6	R.B.	28 F	15	140/90	0	0	Good 35 U	Moderate	30 mg. - 2 mos. 100 mg. - 3 mos. 200 mg. - 7 mos.	12	More hemorrhages appeared
7	V.G.	60 F.	1/2	150/80	0	120	Good 26 U	Moderate	15 mg. - 11 mos. 150 mg. - 5 mos.	16	No apparent change in retinal hemorrhages
8	L.B.	48 F.	4	150/80	0	0	Good	Early	30 mg. - 4 mos. 100 mg. - 5 mos. 200 mg. - 3 mos.	12	No retinal hemorrhages developed in right eye. Retinal hemorrhage in left eye persisted
9	C.N.	63 F.	10	160/60	45	64	Fair 30 U	Early	5 mg. - 3 mos. 10 mg. - 4 mos. 75 mg. - 11 mos. 100 mg. - 4 mos.	21	Cataract in right eye. Retinal hemorrhages in left eye persisted. No fresh hemorrhages appeared
10	J.N.	57 M	5	160/100	45	0	Good 20 U	Moderate	25 mg. - 2 mos. 30 mg. - 1 mo 150 mg. - 4 mos 100 mg. - 6 mos	13	No apparent change in retinal hemorrhages
11	N.M.	47 F	1	160/90	N	N	Fair 40 U	Early	200 mg. - 6 mos 100 mg. - 1 mo	7	Punctate hemorrhages did not absorb. No fresh hemorrhages appeared
12	L.J.	60 F	8	190/105	32	20	Good 10 U	Early	40 mg. - 7 mos No treatment-7 mos 100 mg. - 4 mos	11	Hemorrhages absorbed and H M C was stopped. Punctate hemorrhages reappeared and absorbed again after H M C was given
13	L.G.	62 F	2	140/80	56	0	Good 20 U	Moderate	100 mg. - 1 mo 200 mg. - 4 mos	5	Punctate hemorrhage and cotton wool exudate in left eye absorbed
14	A.D.	66 F	12	150/90	150	150	Good 15 U	Moderate	90 mg. - 2 mos 150 mg. - 2 mos	4	Absorption of some hemorrhages in both eyes
15	T.T.	49 F.	15	130/60	N	N	Good 35 U	Moderate	100 mg. - 5 mos 200 mg. - 6 mos.	11	Absorption of cotton wool exudate and some hemorrhages in both eyes
16	L.M.	33 F.	6	140/60	N	N	Poor 70 U	Moderate	15 mg. - 2 mos. 30 mg. - 2 mos 60 mg. - 1 mo 150 mg. - 3 mos 200 mg. - 2 mos	10	Many hemorrhages absorbed when dosage of H M C was increased to 150 mg daily
17	G.B.	40 F.	21	150/80	66	20	Fair 35 U	Early	15 mg. - 1 mo 50 mg. - 4 mos. No treatment-7 mos. 15 mg. - 2 mos 75 mg. - 2 mos 150 mg. - 2 mos	11	Hemorrhages absorbed and H M C was stopped. Hemorrhages reappeared and persisted after H M C was given again
18	N.R.	74 M	7	140/80	N	N	Good 30 U	Moderate	15 mg. - 16 mos 100 mg. - 5 mos. 200 mg. - 6 mos.	27	Hemorrhages and waxy exudates increased in right eye. Hemorrhages increased in left eye but began to absorb when dosage was increased to 200 mg daily
19	E.R.	30 F	16	110/70	50	8	Fair 15 U	Early	20 mg. - 7 mos 40 mg. - 14 mos 200 mg. - 2 mos 100 mg. - 2 mos.	25	Hemorrhages increased but some absorbed after daily dose was increased to 200 mg
20	W.R.	73 M	10	140/70	N	N	Good 42 U	Early	15 mg. - 12 mos 200 mg. - 4 mos	16	Punctate hemorrhages absorbed and fresh ones appeared
21	A.Y.	48 F	1	155/90	N	N	Good 34 U	Moderate	150 mg. - 7 mos. 100 mg. - 3 mos No treatment-10 mos	15	H M C was stopped after hemorrhages began to absorb. When hemorrhages reappeared treatment was started again without effect
22	M.C.	54 F	14	180/100	20	N	Poor 50 U	Moderate	100 mg. - 1 mo. 150 mg. - 4 mos 150 mg. - 27 mos	27	No apparent change for 2 years. Then hemorrhages appeared to be absorbing

orrhages is known to occur.

In 6 patients (Cases 17 to 22) there was no correlation between the administration of hesperidin methyl chalcone and the absorption of hemorrhages. In Cases 17 and 21, where the patient was used as his own control, improvement could not be duplicated when hemorrhages reappeared after administration of the drug was discontinued. Case 20 showed absorption of pin-point hemorrhages temporal to the disk, but while still receiving treatment a light shower of punctate hemorrhages appeared around the macula.

Using the capillary fragility test as an index of capillary integrity, 9 patients were found to be normal. Of the 18 having increased capillary fragility, 9 showed improvement, 2 were unchanged, and 2 became worse after taking hesperidin methyl chalcone. There were 3 patients (Cases 2, 3, and 5) whose retinopathy increased even though there was a marked reduction in their capillary fragility.

**Discussion.** There is good evidence that diabetes does affect capillaries. Ballantyne<sup>2</sup> has demonstrated the presence of retinal capillary aneurysms which he regards as the earliest sign of diabetes in the fundus. The aneurysms resemble punctate hemorrhages, but can be differentiated from them with the ophthalmoscope. Friedenwald<sup>1</sup> has shown that in some cases the aneurysm may be incompletely lined by endothelium and suggests that the initial process may be a break in the capillary wall through which blood escapes forming a punctate hemorrhage. The red cells may then be enveloped by endothelial cells forming a minute sacular aneurysm. Hanum<sup>3</sup> reported that diabetics with hemorrhagic retinopathy showed increased capillary fragility. Other investigators have also been able to demonstrate that capillary fragility is greater in diabetics with hemorrhagic retinal lesions than in diabetics who do not show a retinopathy.

The process by which diabetes damages capillaries is still unknown. Whether the damage causes increased capillary fragility or permeability or both also remains undetermined. Therapeutic use of vitamin P in retinal hemorrhages is based on the concept that this vitamin is an important factor in maintaining normal capillary permeability. McLean<sup>11</sup> reported improvement in 2 diabetics who received dicumarol and rutin. Shanno, *et al.*<sup>17</sup> studied a group of patients with diabetic retinopathy who received 60 mg. rutin daily. They could not reach definite conclusions but suggest that rutin might prevent further retinal hemorrhages.

If the concept that diabetes injures capillaries, thereby causing retinal hemorrhages, is valid; then any therapy which improves or restores the integrity of the capillary wall should prevent further hemorrhages and probably aid in the absorption of those already present. Since almost 70% of the patients with abnormal petechial indices were improved, it would seem reasonable to attribute the improvement in capillary permeability or fragility to the administration of hesperidin methyl chalcone. However, the improved state of the capillaries as indicated by fragility tests was not reflected by corresponding improvement in retinal hemorrhages and this is the most important consideration.

There were 6 patients (Cases 1 to 6) who showed a definite increase in the number of hemorrhages. In another group (Cases 17 to 22) there was no definite correlation between therapy and the course of the retinopathy. Some hemorrhages absorbed while fresh ones appeared. These 12 patients presented a progressive change in retinal lesions which was apparently not influenced by taking hesperidin methyl chalcone. In 5 patients (Cases 7 to 11) the retinopathy remained stationary and in these instances the administra-

tion of hesperidin methyl chalcone may have prevented any fresh retinal lesions from appearing. Where there was evidence of improvement (Cases 11 to 17), hesperidin methyl chalcone may have played some part in the absorption of retinal hemorrhages. It should be emphasized again that the retinopathy of diabetes does show spontaneous changes.

**Conclusions.** A group of diabetic patients was studied to determine the effect of vitamin P on diabetic retinopathy. As part of the study prothrombin time and capillary fragility were measured. The level of plasma proteins was also determined. Although the number of patients observed over a sufficiently long period was not large, the following conclusions seem justified.

1. There was no significant alteration in the plasma albumin or globulin of 23 diabetics. All but 3 had some evidence of diabetic changes in the retina.

2. The prothrombin time tended to increase in those patients whose known duration of the disease averaged 10 years. As would be expected these patients also showed more extensive changes in the retina. The relationship,

if any, between prothrombin time and diabetic retinopathy deserves further study.

3. About 50% of the cases of retinopathy in this group displayed increased capillary permeability, as manifested by the petechial index. There did not appear to be any correlation between capillary permeability and prothrombin time.

4. The petechial index improves in many cases after the administration of vitamin P, suggesting that this vitamin has some effect on capillaries. In most patients where this was observed there was no significant alteration in the appearance of retinal hemorrhages. Retinal hemorrhages are seen in diabetics who do not show increased capillary fragility.

5. Vitamin P did not alter the course of diabetic retinopathy in a majority of these cases. There were 6 whose lesions progressed, 5 who showed improvement, while 5 others have benefited, since no fresh lesions appeared. Any favorable effect attributed to vitamin P must take into consideration the possibility of spontaneous changes in retinal lesions of diabetes.

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# THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION: ITS VALUE AS A DIAGNOSTIC AID IN 130 AUTOPSIED CASES\*

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THE electrocardiogram has been recognized as an aid in the diagnosis of myocardial infarction for almost 30 years. During this period there have been numerous reported instances and countless unreported cases in which diagnosis was established during life by the electrocardiogram and later confirmed at autopsy. There have been many other instances—less often reported—in which an electrocardiographic diagnosis of myocardial infarction was not confirmed at subsequent autopsy. There have, however, been surprisingly few reports evaluating the electrocardiographic diagnosis of myocardial infarction in a large series of consecutive cases.<sup>1,5,6,7,8,12</sup> It is the purpose of this article to report the electrocardiographic findings in a considerable group of cases of myocardial infarction and to evaluate the electrocardiogram in the diagnosis of this disease.

**Method:** Cases used in this study were those that died and were autopsied at this hospital during the 3 year period from April 1, 1945 to April 1, 1948. These cases fall into 2 groups, the first group being composed of all patients autopsied during the 3 year period on whom there was a pathological diagnosis of myocardial infarction. The second group is composed of those cases on whom a clinical diagnosis of myocardial infarction was made positively or was considered first among multiple diagnoses and on whom subsequent pathological study failed to confirm the diagnosis. (This study is concerned with infarctions of the ventricular

myocardium only. Infarctions of the auricles were not noted or recorded in review of the autopsy data, and in this article the term "myocardial infarct" refers to infarcts of the ventricles only.)

In the vast majority of these cases no special sectioning or injection techniques were employed. The autopsy diagnosis of myocardial infarction was made in most instances by observation of the gross specimen with subsequent confirmatory microscopic study. In a few instances of very early infarction only microscopic myocardial changes were present when a coronary occlusion was apparent on gross examination. With one exception all of the cases of myocardial infarction included in this series showed infarcts at least 1 cm. in diameter, and the many cases showing multiple microscopic infarcts or small fibrotic patches were excluded from the group judged to show infarcts. Similarly cases showing only very small infarcts seen only on microscopic study were included among the cases that were considered not to show infarcts, and it is recognized that by routine methods similar infarcts may completely escape observation. By this means it was hoped to restrict the cases included to those infarcts that could reasonably be supposed to be diagnosed by ECG study. Unless otherwise described all infarcts extended through a full thickness of ventricular wall.

The ECG policy employed at this hospital during the period covered by this study may be briefly summarized. Routine ECGs taken on patients hospitalized included the 3 "standard" leads (I, II, and III) and an additional single chest lead taken with the exploring electrode at position 4. This lead was usually CF<sub>4</sub>, occasionally V<sub>4</sub>.

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FAILEY: ELECTROCARDIOGRAM IN MYOCARDIAL INFARCT

TABLE 1. PATIENTS WITH PROVED ANTERIOR MYOCARDIAL INFARCTS ON WHOM ONE OR MORE ECGs WERE TAKEN.

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Kind of infarct found
RECENT INFARCTS					
5	Pos.	4	Left vent. preponderance.	In CF <sub>4</sub> ; doubtful Q wave, ST segment up 1-2 mm., doubtful T wave inversion.	Large early ant.
10	Neg.	4, 4	Sinus tachycardia.	In second CF <sub>4</sub> , small Q, small jagged R, then deep S. No segment shift, T inversion.	Large early ant.
11	Pos.	4	A-V block, RBBB.	In CF <sub>4</sub> , ST segment up 2 mm., beginning inversion of T.	Rec. ant. 3 cm. in diam.
12	Neg.	4, 4	Vent. tachycardia.	Vent. tachycardia on first record. Diagonal T in leads II and CF <sub>4</sub> on second record.	Rec. high ant-septal 3 cm. in diam.
13	Pos.	12, 4	Ant. infarct.	Multiple precordial leads showed small R waves, deep S, ST segment up 2 mm. with T starting to invert. Later same day CF <sub>4</sub> showed Q.	Massive ant.
19	Pos.	4, 4	Ant. infarct.	In CF <sub>4</sub> , small R, deep S, ST slightly elevated, T inverted.	Large ant.
21	Neg.	4, 4	Ant. infarct.	In CF <sub>4</sub> , small R, deep S, ST slightly elevated, T inverted.	Rec. large ant. and septal.
23	Pos.	4	Runs of vent. tachycardia, RBBB.	Same. No specific changes of infarction.	Red. and old near apex, 4 cm. in diam.
24	Pos.	4, 12	Ant. infarct. Left BBB.	In CF <sub>4</sub> , small R, elevated ST segment, inverted T. Second ECG showed LBBB.	Large ac. ant.
30	Pos.	4, 4	Ant. infarct.	In CF <sub>4</sub> , large Q, elevated ST, inverted T. Inverted T also in leads I, II.	Rec. ant. 3 cm. in diam.
34	Pos.	4, 4	Complete A-V dissociation.	In CF <sub>4</sub> , large Q, elevated ST inverted T.	Large ac. ant.
38	Pos.	4, 4	Aur. fibrillation.	In both ECG's CF <sub>4</sub> showed R almost absent, elevated ST, inverted T. Also RBBB.	Rec. sub-endo-cardial (at apex, 1 cm. in diam.).
39	Neg.	4, 4	Wolff-Parkinson-White type BBB.	Aur. fibrillation. Inverted T in CF <sub>4</sub> .	Rec. ant. apical 4 cm. in diam.
51	Neg.	4, 4	LBbB(x3). Ant. infarct.	Otherwise normal.	Rec. ant. 2 cm. in diam.
52	Neg.	4	LBbB(x3). Ant. infarct.	Same. No evidence of infarction changes.	Ant. septal 3 cm. in diam.
53	Pos.	4, 4, 12, 4	RBBB, ant. infarct.	R small or absent in CF <sub>4</sub> . No ST or T change. Low T in lead I.	Large ac. ant.
68	Pos.	9	Aur. fibrillation, right axis deviation, digitalis effect.	First 3 ECG's showed LBbB. Last showed Q wave, elevated ST, inverted T in CF <sub>4</sub> .	Rec. ant. 3 cm. in diam.
72	Neg.	4	Ant. infarct, RBBB.	Large Q in CF <sub>1</sub> through 6 with ST elevated 1 to 5 mm.	Acute ant. septal 3 cm. in diam.
73	Pos.	12	Ant. infarct.	Same. No evidence of infarction.	Old, large ant.
75*	Pos.	4	Somatic tremor	Elevated ST, inverted T in leads V <sub>1</sub> , V <sub>2</sub> , V <sub>3</sub> , aV <sub>1</sub> but not in lead I. No Q.	Acute apical, 3 cm. in diam.
79	Pos.	4	"Non-specific abnormal record."	Large Q, elevated ST in CF <sub>4</sub> . No T wave inversion.	Large ac. ant.
87	Neg.	4, 4	Ant. infarct.	Same. No changes demonstrating infarction.	Large ac. ant.
88	Pos.	4	Ant. infarct.	Same. No changes demonstrating infarction.	Large ac. ant.
89	Pos.	4	Left vent. preponderance.	CF <sub>4</sub> showed large Q, ST elevated 3 mm.	Large ac. ant.
90	Neg.	4, 4, 4, 4	Left vent. preponderance.	Small R wave, ST elevated 5 mm., T wave inverting in CF <sub>4</sub> .	Rec. ant. septal 1 x 3 cm. in area.
96	Pos.	4	Ant. infarct.	Same. No changes demonstrating infarction.	Rec. large ant.
98**	Pos.	4, 4, 4	Ant. infarct.	Large Q, elevated ST, inverted T in CF <sub>4</sub> in every instance.	Large ant. aneurysm, no infarct.
41	Neg.	4	Left vent. preponderance.	OLD INFARCTS	Old ant. at apex, 2 x 4 cm.
46	Neg.	4	Left vent. preponderance.	In CF <sub>4</sub> wide but shallow Q, no ST or T change.	Old apical, 3 cm. in diam.
86	Neg.	4	Left vent. preponderance (x2). Ant. infarct (x2).	ECG not available.	Old apical, 2 x 3 cm.
97	Neg.	4, 4, 12, 4	Left vent. preponderance.	Flat T wave in CF <sub>4</sub> is only abnormality.	Old, large ant-septal.

\* Case 75 in hospital twice for myocardial infarction.

\*\* Case 98 in hospital twice, once for infarction.

When additional leads were thought to be indicated (either by the clinicians or by the electrocardiographer) these were taken either as part of the initial ECG or in subsequent tracings. The additional leads most frequently taken were multiple chest leads with the exploring electrode placed in the 6 positions commonly used today and the 3 unipolar extremity leads.<sup>3,11,13</sup> Other chest and unipolar leads were taken infrequently and irregularly, so that in this study they have neither been reported nor analyzed. Usually ECGs taken as emergencies were read first by residents on the wards who were familiar with patients' clinical findings. All ECGs were subsequently seen by a junior resident assigned to the ECG service and again by one or more of four staff men each of whom has had several years' experience in clinical cardiology and ECG interpretation. Electrocardiographers were as a rule not familiar with patients' clinical findings and history. In consequence, ECGs were read initially without the availability of clinical information but were checked later against a brief clinical note on the ECG request slip. Since ECGs once read were sent to the wards and bound with patients' charts, they were usually not examined by the electrocardiographers when serial tracings were taken, although a note of previous ECG findings frequently accompanied requests for subsequent tracings.

In reviewing cases in this study the procedure employed was as follows: After pathological reports, charts, and ECGs on all patients were assembled, a patient's ECG was first examined by the author and tentative diagnosis made. This was then checked with the official hospital ECG diagnosis, then with the patient's clinical chart, and finally with the autopsy report. In cases where there was apparent disparity among any of these reports or when the author had previous familiarity with any aspect of the case, the material was reviewed by one or more of the staff electrocardiographers. By this means it was hoped that analysis of the data would be made impartially and that initial ECG interpretations would be uninfluenced by knowledge of clinical or pathological data.

The system employed by the hospital in coding charts and the system for filing ECGs undoubtedly excluded several cases that would ideally have been included in this study. These cases are in the main those on which on ECG diagnosis of myocardial infarction was made several months before the patients' death, and not confirmed at autopsy. Since cases were collected initially through the pathology department rather than from the ECG files or the record room, it is probable that several cases were excluded because myocardial infarction was not mentioned in the death note diagnosis or found at autopsy, although the diagnosis might have been made in some earlier ECG reading.

**Results:** *A. Cases with myocardial infarction proved at autopsy.* In this group were 100 cases having an average age of 63.3 years. This included a range from 15 to 90 years, the youngest patient being a colored male with infarction resulting from a luetic ostial occlusion. These 100 cases included 67 males and 33 females; 87 patients were white and 13 colored. In the entire group 45 cases were either never studied electrocardiographically or had ECGs taken at a time which review of all data suggested was prior to the development of myocardial infarction.

Among the 100 cases of proved myocardial infarction, 55 were studied with one or more ECGs taken at times when they should be expected to record the changes produced by myocardial infarction. The data from these cases are presented in Tables 1, 2, and 3. One of these cases (Case 75) was hospitalized twice with a diagnosis of myocardial infarction and so is listed twice in the tables. In these tables the notation "4 leads" means that 3 standard leads and a CF or V4 lead were taken, "9 leads" means that 6 precordial leads were taken in addition to the 3 standard leads, and "12 leads" means that 3 standard leads, 6 precordials, and 3 unipolar extremity leads



employing the Goldberger technique were taken.

The data in these tables have been grouped according to the site of the infarct demonstrated at autopsy. Referring first to the acute infarcts on the anterior surface of the heart (Table 1) it may be seen that there were 27 of these. Of these 27, 13 (48%) were diagnosed electrocardiographically. Review of the ECG findings and correlation with pathological data reveals no instance in which the ECG changes that were attributed to the infarction might reasonably be supposed to arise

from some other cause. Of the total group of 27 cases, 9 had no recorded history suggesting acute coronary disease. None of these 9 cases was studied by more than the minimal 4 leads. An ECG diagnosis of infarct was made in only 1 (11%) of these 9 cases. Review readings of the ECGs in these cases show 2 additional instances (Cases 10 and 52) in which changes in CF4 were probably due to the underlying infarct.

Of the 18 anterior infarct cases with a history positive for acute coronary disease 12 (67%) were diagnosed elec-

TABLE 2. PATIENTS WITH PROVED POSTERIOR MYOCARDIAL INFARCTS ON WHOM ONE OR MORE ECGs WERE TAKEN

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Kind of infarct found
RECENT INFARCTS					
9	Pos.	12	Post. infarct.	Lead III of small voltage composed of Q or QS 2 mm. deep and .04 sec. wide; aVf composed of small R, no Q; ST depressed 3 mm. in V3 and V4.	Rec. large post. near septum.
14	Pos.	9	Post. infarct.	Large Q3 with inverted T wave. Pre-cordial leads not remarkable.	Rec. post. near septum, 3 x 4 cm. in area.
15	Neg.	12, 12	Post. infarct.	Large Q3 with inverted T wave. Height of R wave in aVf diminished in progressive ECG's.	Rec. post. 3 cm. in diam.
18	Pos.	4	Post. infarct.	ECG not available.	Ac. post. 3 cm. in diam.
20	Neg.	I, II, III, CF <sub>2</sub> , CF <sub>4</sub> , CF <sub>5</sub>	Sinus tachycardia.	Sinus tachycardia. Large Q2 and Q3 without ST or T wave change. Pre-cordial leads not remarkable.	Rec. 4 x 4 cm. post.
33	Pos.	9, 4	Post. infarct.	Large Q2 and Q3 with ST segments greatly elevated.	Rec. large post.
63	Pos.	4	Post. infarct.	Large Q2 and Q3 with ST segments greatly elevated and T waves inverting.	Rec. post. 3 cm. in diam. near septum.
66	Neg.	4	Ant. infarct.	No ECG change specifically attributable to infarction in leads II or III. CF4 showed very small R, ST elevated 2 mm., absent T.	Rec. post. 3 x 4 cm.
75*	Pos.	4	Post. infarct.	Q2 and Q3 present with ST elevated 2 mm. and T wave inverting. Changes of previous anterior infarct seen in CF4.	Rec. large post. near septum.
77	Pos.	12	Post. infarct.	Q wave present in II, III, aVf with ST elevated 1 mm. V3 and V4 showed R wave almost absent with ST segment elevated 4 mm.	Rec. 3 x 4 cm. post. at septum near apex.
80	Pos.	4	"Abnormal record."	Large Q3 with no ST shift and upright T wave.	Rec. post. 0.5 x 1 mm. high, near septum.
83**	Pos.	4, 4, 12	Post. infarct, Compl. A-V block.	ST elevation, T wave inversion in II, III, aVf. No Q waves. Compl. A-V block.	Old post. 3 cm. in diam. near septum.
95	Pos.	12, 4, 4	Compl. A-V block, RBBB.	Large Q in II, III, aVf with deeply inverted T wave. Precordials showed RBBB.	Large rec. post.
OLD INFARCTS					
7	Neg.	4	"Abnormal record."	Low voltage in all standard leads. No changes demonstrating infarction.	Old 3 x 4 cm. post. near septum.
99	Neg.	4	"Abnormal record."	No changes demonstrating infarction.	Old post. 4 cm. in diam.

\* Case 75 in hospital twice for myocardial infarction.

\*\* Case 83 in hospital twice, once for infarction.

trocardiographically. Five of these cases were studied with complete precordial leads, and in all of these cases the infarct was diagnosed by ECG. Review of the tracings on these 5 cases shows only 1 case (Case 73) in which a precordial lead at position 4 should not have suggested the diagnosis.

Of the remaining 13 cases with positive histories but without multiple precordial leads the ECG diagnosis was made in 7 cases (54%). Review readings of the ECGs in these cases show 3 additional instances (Cases 5, 11, 38) in which changes in CF4 were probably due to the underlying infarct. Of the total group of acute anterior infarcts studied with only 4 leads, 8 of 22 (36%) were diagnosed by ECG. This contrasts with 5 of 5 (100%) studied with multiple precordial leads.

Of the 4 cases having infarcts classified as "old" occurring on the anterior surface of the heart 1 (25%) was diagnosed by ECG. None of these cases had a history suggesting coronary disease. The one case in which the diagnosis was made electrocardiographically was diagnosed from a 12 lead ECG. Review of this and the other ECGs taken on this patient reveals changes in the isolated lead 4 which are definitely attributable to the infarct. The diagnosis, however, was made only when the 12 lead ECG was taken. The remaining 3 cases in this group were studied only with the 4 lead ECG. Of these 3 cases review shows changes in lead 4 of 1 case which should have suggested infarction. In a second case the ECGs were not available for review, and in the third case there are no ECG changes which can be attributed definitely to infarction.

There were 13 cases in which pathological study showed posterior infarcts that were classified as acute (See Table 2). Of these 13 cases, 9 (69%) were diagnosed electrocardiographically. Of

these 13 cases 3 had no recorded history of coronary disease, and in these 3 cases the ECG diagnosis was correct in 1 and incorrect in 2. One of the incorrect diagnoses (Case 66) was called an anterior infarct, so that while for clinical purposes the diagnosis can be considered correct, electrocardiographically it is not accurate. The one case with correct ECG diagnosis among these 3 was the only one studied with 12 leads.

Of the 10 cases of acute posterior infarction with histories positive for coronary disease the ECG diagnosis was made in 8 (80%). Six of these cases were studied with no more than 4 leads and with 5 correct ECG diagnoses. Four were studied with 12 leads with 3 correct ECG diagnoses. In the entire group of 13 cases, 5 of 8 (63%) correct ECG diagnoses were made when 4 leads were used and 4 of 5 (80%) when 12 leads were used.

Of the 2 cases of posterior infarction classified as "old," both were studied with 4 lead ECGs only. Neither had a history positive for coronary disease, and neither was diagnosed electrocardiographically.

The remaining cases of proved infarction (Table 3) are too few for any statistical analysis to be attempted. High lateral infarcts are grouped separately because of the special problems involved in their ECG diagnosis.<sup>10</sup> The 3 cases in the group of multiple infarcts are not well classified elsewhere. The cases of isolated right ventricular infarcts, left bundle-branch block, and ventricular tachycardia are grouped separately because infarcts in these categories are generally considered impossible of diagnosis by electrocardiographic means.

*B. Cases with myocardial infarction not proved at autopsy.* In this group were 30 cases having an average age of 58.3 years. This included a range from 29 to 78 years. In this group

of patients were 26 males (86%) and 4 females (14%); 24 (83%) were white and 6 (17%) were colored. These cases represented patients dying of a fairly wide variety of diseases. Most of them were hospitalized for relatively short periods of time or died suddenly and unexpectedly while in the hospital. The common factor among them is that in every instance a final clinical diagnosis of myocardial infarction was stated positively or was regarded as a probable first choice among several possibilities. In none of these cases was the diagnosis of myocardial infarction substantiated by post mortem examination.

The data on these cases are tabulated in Table 4. It may be noted that of the total of 30 cases 14 were not studied by any ECG that was pertinent to the terminal event. In the remaining 16 the ECG was not read as suggestive of infarction in 10 cases but was read as such in 6 cases. The itemized presentation of these 6 cases shows that in 3 instances a clinical diagnosis of myocardial infarction was not made or considered probable until it was influenced by an ECG diagnosis of infarction. In the other 3 cases an ECG diagnosis of infarct tended to confirm an already erroneous diagnosis.

**Discussion:** A study such as this one which is based on the collection of a number of hospital cases, many representing patients who were not the objects of special study during life, must of course raise problems which are not answered. From the review of material on the 100 cases of proved myocardial infarction several observations are suggested. The first of these is that of the total number of patients with myocardial infarcts only about half (55%) will receive an ECG study at

such a time that their infarction can be demonstrated electrocardiographically. This percentage could undoubtedly be increased without great change in current hospital procedure; but for the figure to approach 100% it would seem necessary to make an ECG study almost a routine procedure on all patients or at least all beyond early adult life.

Of the 55 patients (56 cases) with myocardial infarction there were 2 who showed left bundle-branch block in all ECGs taken and 1 with ventricular tachycardia. This amounts to about 5% of all cases, and in these cases the ECG can be of no positive help in regard to infarcts, as the changes produced by left bundle-branch block and ventricular tachycardia, according to contemporary electrocardiographic theory, will completely obscure those resulting from infarction of the ventricles.<sup>14</sup> Similarly isolated right ventricular infarcts are not thought to be amenable to specific ECG diagnosis. In this series there were 2 of these infarcts. Although 1 (Case 40, Table 3) was diagnosed on the ECG, its localization was not correct. For the purposes of this study these should probably be included in the group of those which cannot be diagnosed electrocardiographically.\* Added to the cases just mentioned, this would bring up to 9% the number of cases in which the ECG was of no specific diagnostic aid.

Among the total of 56 cases there were 29 (52%) diagnoses of myocardial infarction including as correct diagnoses the few cases in which the localization of the infarct was obviously erroneous. Among the cases with a history positive for coronary disease the figure was 24 in 33 (73%). Among the cases with a negative history there

\* The author can find no clear statement in the literature as to electrocardiographic correlation with infarcts of the right ventricle. However, the relative electrical positivity of the interior of the right ventricle during the early part of the QRS complex in the normal heart theoretically prevents the development of a Q wave in isolated infarction of the right ventricle.

were 5 diagnoses in 23 cases (22%). The reasons for this disparity would appear to depend chiefly on the following factors: the size of the infarct, the frequency in the use of multiple leads beyond the minimal 4, and the degree of influence that a positive history may have on the individual making the ECG interpretations.

gested the presence of infarction, and as has been shown these made a considerable contribution in establishing the diagnosis by ECG. The subjective element is more difficult to evaluate. As described earlier, the ECG policy employed at this hospital is planned so as to eliminate as far as possible the influence of clinical data on the initial

TABLE 3. MISCELLANEOUS PROVED MYOCARDIAL INFARCTS

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Kind of infarct found
HIGH LATERAL INFARCTS					
62	Pos.	I, II, III, CF <sub>2</sub> , CF <sub>4</sub> , CF <sub>6</sub>	Ant. infarct.	In CF <sub>4</sub> very narrow Q 3 mm. deep; inverted T wave. In standard leads no changes demonstrating infarction.	Rec. high post.-lat. 3 cm. in diam.
100	Pos.	4, 12	High ant.-lat. infarct.	First ECG non-contributory. Second showed small Q in I, V <sub>6</sub> , large Q with inverted T wave in aVI.	Rec. high post.-lat. 4 cm. in diam.
MULTIPLE INFARCTS					
16	Neg.	4	"Abnormal record."	Low voltage in standard leads. CF <sub>4</sub> showed nor. R, deep S wave.	Old large ant-septal, rec. large high post.-lat. Of entire intervent. septum with perf.
74	Pos.	1, 4, 12	Post. and septal infarct.	Large Q <sub>2</sub> and Q <sub>3</sub> with inverted T waves. Large Q in V <sub>1</sub> , V <sub>2</sub> , V <sub>3</sub> .	Many small; of entire Intervent. septum.
94	Neg.	4	Post. infarct.	Low voltage lead III with small Q wave; sl. T wave inversion.	
RIGHT VENTRICULAR INFARCTS					
8	Neg.	4	Digitalis effect.	Same. No changes demonstrating infarction.	Old post. of right vent., 2 x 4 cm. in area.
10	Pos.	4	Post. infarct.	ST <sub>2</sub> and 3 elevated 1 mm.; early inversion of T waves in these leads.	Early ant. of right vent. 2 x 3 cm. in area.
ELECTROCARDIOGRAMS SHOWING LEFT BBB ONLY					
6	Pos.	4, 4	Left BBB.	Same.	Old and rec. ant.
50	Neg.	1, 1, 1	Left BBB.	Same.	Old and rec. post.
ELECTROCARDIOGRAMS SHOWING VENTRICULAR TACHYCARDIA ONLY					
31	Neg.	1, 1, 4, 1	Vent. tachycardia.	Same.	Old large ant. vent. aneurysm. No infarct.

The pathology reports used in this study did not always have recorded the exact measurements of the infarcts described, so that no specific conclusions can be drawn as to exact size. Rough observation of the data in this report shows no apparent correlation between the size of the infarct and the presence of a history suggestive of infarction. Review of other literature on myocardial infarction confirms this observation.<sup>2</sup> Among the cases described in this report multiple chest leads and unipolar extremity leads were more often taken when clinical findings sug-

gested the presence of infarction, and as has been shown these made a considerable contribution in establishing the diagnosis by ECG. It is difficult to believe, however, that this influence is completely eliminated. As an example, it is difficult to imagine how an individual could be confronted with a 12 lead emergency ECG and not search carefully for indications of myocardial infarction.

The percentage of correct ECG diagnoses in anterior infarcts (48% in acute cases, 45% in all) is considerably inferior to the percentage in posterior infarcts (69% in acute cases, 60% in all). The 100% of correct diagnoses in cases of anterior infarction where 6 precordial

leads were taken suggests that anterior infarcts are much more frequently diagnosed by this technique. There were only 6 cases in this group. They may have been in some measure selected cases from a clinical standpoint, and review of the ECGs indicates that some of these cases should have been diagnosed from a precordial lead taken at position 4 alone. By way of contrast, however, are the 2 cases showing changes in isolated CF4 leads almost certainly due to infarction which were missed on the initial reading. There are in addition a few other cases where changes in the single precordial lead are probably due to infarction, and there are also several cases in which

relationship of the precordial electrode to the heart. The several examples in this paper of small R waves in lead CF4 almost without question include instances where the single precordial lead was placed more over the right ventricle than over the left. This is also illustrated by the cases in Table 4 which were misdiagnosed as anterior infarcts by virtue of small or absent R waves in CF4. It might also be mentioned that none of the proved cases of infarction in this series showed a type of precordial pattern that is so often read as suggestive of infarction. This pattern is that of absent R waves in the precordial leads taken at positions C1 and sometimes C2 with a pro-

TABLE 4. INFARCTS DIAGNOSED CLINICALLY AND ELECTROCARDIOGRAPHICALLY WHICH WERE NOT FOUND AT AUTOPSY. SUMMARY OF CASES WITH POSITIVE DIAGNOSIS OF INFARCTS.

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Autopsy findings
109	Neg.	4	Ant. infarct, left vent. preprod.	Very small R wave in CF4 with ST segment elevated 3 mm. and T wave inverting. Left vent. preprod. in standard leads.	Chr. passive cong. Mult. pul. infarcts.
110	Neg.	4, 4	Ant. infarct, left vent. preprod.	Absent R wave in first CF4, very small R wave in second. No ST shift. T waves upright. Left vent. preprod. in stand leads. ECG not available.	Perf. duodenal ulcer; peritonitis.
113	Neg.	4	Ant. infarct.		Gangrene of lower esophagus.
127	Pos.	4, 12, 4	Post. infarct, nodal tachycardia.	Small Q wave in lead III but not in II or a VI. All records showed tachycardia, prob. nodal, poss. vent.	Cbr. fibroid tuberc.
129	Pos.	4	Post. infarct.	Large Q3 with elevated ST segment and inverted T wave. Lead 1: large S wave.	Widespread lobar pneumonia.
130*	Pos.	12	Ant. infarct.	Elevated ST segments in all precordials, lead I, lead aVI. No Q waves, no T wave inversion.	Hemoperic. due to ruptured aor. aneurysm.

\* Case 130 is the same patient as case 83 in Table 2.

very large anterior infarcts found at autopsy were missed by a single precordial lead where there is every reason to suppose that multiple leads would have shown changes due to infarction. An additional factor in this regard is the variability in placing of the precordial electrode. In obese patients and in patients with chest deformities due to emphysema it is frequently impossible to be sure of the

progressive rise in the height of R as the electrode is moved over the left chest.

Contrasting with the situation seen in anterior or antero-lateral infarction the "posterior" surface of the heart, lying for the most part on the diaphragm, does not permit easy exploration with multiple leads. Esophageal leads are relatively impractical and difficult to apply, particularly in seriously ill patients. Multiple exploring leads

over the back, the subject of current research in several institutions, do not lend themselves to such easy interpretation as do leads over the anterior chest. By way of compensation, however, lead III is of considerably more value in diagnosing posterior infarcts than is lead I in anterior infarction. Similarly lead aVf is considerably more valuable than an isolated lead aVl. This point is aptly illustrated by the data in the tables, where the ECG patterns in leads I and aVl were so infrequently of diagnostic aid that they are tabulated in only a few cases.

In view of the difficulty in distinguishing the Q waves and inverted T waves of lead III caused by posterior infarction from those which are due to position alone it appears somewhat remarkable that such a high percentage of these cases were diagnosed correctly. It is quite probable that if our filing system had enabled the author to review all the ECGs upon which a diagnosis of posterior infarction had been based, several instances of erroneous diagnosis of posterior infarction would have been discovered which were missed because the patients died from other causes at a considerable time after this ECG diagnosis had been made. The small number of cases in Table 4, however, which were mistakenly called posterior infarction tends to discount this observation.

One aspect of the diagnosis of posterior infarction which seemed rather striking was the negligible value of lead aVf in differentiating "normal" from pathological Q waves in lead III.

Recent studies, notably those of Goldberger<sup>1</sup> and of Myers and Oren,<sup>9</sup> have emphasized the value of this lead in the diagnosis of posterior infarction. It is true that of the 5 cases of posterior infarction in this study in which lead aVf was taken the diagnosis was made in 4 and that the fifth (Case 95, Table 2) represents perhaps the outstanding error of interpretation in all the cases presented here. Review of the tracings in these cases, however, shows no instance where the diagnosis was clearly presented in lead aVf but not seen equally well in lead III. The only exception to this statement might be provided by Case 15 (Table 2) where the height of the R wave in aVf diminished in progressive tracings.\*

Another interesting aspect of the diagnosis of posterior infarction is seen in Cases 7, 66, and 99 of Table 2. These cases all had infarcts of moderate size, but in none of them were there any changes in lead III to suggest infarction. With the thought that perhaps extreme vertical position of the heart within the thoracic cavity coupled with clockwise rotation on the long axis might prevent these ECG changes from being referred to the diaphragm and the left leg the records on these cases were reviewed carefully. Chest films had been taken on two of the three cases, and review of these along with the recorded physical examinations and autopsy findings of all three cases showed no marked pulmonary lesion or chest deformity which might significantly shift the position of the heart within the chest.

\* This rapid diminution in the height of an R wave in lead aVf—or for that matter in lead III—would appear to be a useful change to observe and one suggestive of posterior infarction. In the horizontally placed heart the foot electrode records the sum of the potential variations of the diaphragmatic surface of the heart. In the case of a small infarct of this surface or one so placed that its full electrical effect is not recorded by the foot electrode a Q wave may not appear on the tracing in lead aVf but the overall reduction in positive potential may reduce the height of the R wave in aVf. If before infarction the ECG of this heart showed an extremely small R wave in lead III due to position alone, the change in potential resulting from the infarct might be sufficient to cause a Q wave in lead III but not aVf. This Q3 is in a sense not the result of myocardial infarction but of infarction plus the effect of the heart's position within the chest. This apparently has occurred in this instance (Case 15, Table 2).

Of the 5 cases in which infarction was erroneously diagnosed by ECG and on which tracings were available for review (Table 4), 2 were clearly diagnosed on the basis of a small or absent R wave in a single precordial lead. In these cases multiple chest leads would almost certainly have clarified the picture sufficiently for a mistaken diagnosis of infarction to be avoided. One case was misread as a posterior infarct due to the presence of a large Q3 with elevated ST segment and inverted T wave. Review of this ECG shows it to be typical of posterior infarction in almost every respect except perhaps that it has a large S wave in lead I. It is possible that a lead aVf might have helped in making a correct diagnosis but the evidence presented earlier in this paper does not indicate that this is likely. Another case in this group was diagnosed wrongly as posterior infarct because of the distorting effect of a probable nodal tachycardia. The final case represents a pure error in interpretation, as review of the ECGs from this patient shows them to be typical of very acute pericarditis and not of acute infarction. In this entire study, which includes only autopsied patients, cases in which 6 precordial leads were taken were misdiagnosed electrocardiographically only through errors in interpretation and not because of insufficient data. The same might not necessarily be true in non-fatal disease.

**Summary and Conclusions.** 1. One hundred cases of proved myocardial infarction and 30 cases with a clinical diagnosis of myocardial infarction that was not found at autopsy are reviewed with special reference to the place of the electrocardiogram in the diagnosis of this disease.

2. Fifty-five patients with proved myocardial infarction were studied electrocardiographically at times subse-

quent to the development of their infarcts. In these patients myocardial infarction was diagnosed electrocardiographically in 52% of cases.

3. In 22 patients with proved recent anterior infarction the diagnosis was made electrocardiographically in 36% when only 4 leads were taken. In 5 patients with proved recent anterior infarction the diagnosis was made electrocardiographically in 100% when 6 precordial leads were taken.

4. In 8 patients with proved recent posterior infarction the diagnosis was made electrocardiographically in 63% when only 4 leads were taken. In 5 patients with proved recent posterior infarction the diagnosis was made electrocardiographically in 80% when unipolar extremity leads were taken in addition to these.

5. Sixteen patients with a clinical diagnosis of myocardial infarction were studied electrocardiographically. In 6 (38%) of these patients an incorrect electrocardiographic diagnosis of myocardial infarction was made, as infarction according to the criteria adopted was not found at autopsy.

6. Based on an analysis of these records, the use of 6 precordial leads as a routine procedure appears to be of great value in the accurate diagnosis of anterior myocardial infarction and represents a considerable improvement over the technique employing only a single precordial lead. When the multiple lead technique is used, errors in diagnosis will be almost exclusively those of electrocardiographic interpretation as contrasted with errors stemming from insufficient data.

7. The use of unipolar extremity leads appears to be of comparatively little value in the accurate diagnosis of myocardial infarction. Specifically the use of lead aVf appears to contribute little information toward the accurate diagnosis of posterior infarction.

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# NEGATIVE RESULTS OF TOCOPHEROL THERAPY IN CARDIOVASCULAR DISEASE\*

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For many years studies have been carried on in experimental animals to determine the metabolic function of vitamin E in relationship to the reproductive, muscular, and vascular systems. In the rat<sup>1</sup> it has been shown that vitamin E is necessary for reproduction. In the rat, guinea pig, rabbit and hamster, vitamin E deficient diets produce a profound alteration in the skeletal muscles microscopically similar to that found in the human muscular dystrophies.<sup>2,3,6</sup> It has been demonstrated that the oxygen consumption, creatine, and chloride content of muscles in vitamin E deficient animals may be influenced by feeding alpha tocopherol.<sup>6</sup> The clinical applications of these studies, however, have been disappointing. At one time enthusiasm was expressed over the possible value of vitamin E in the prevention of spontaneous and habitual abortion of unknown etiology in humans.<sup>17</sup> The more recent papers have described consistently negative results in the treatment of the muscular dystrophies with vitamin E.<sup>5,9,11</sup> There is ample evidence that the blood level of vitamin E can be raised with tocopherol therapy.<sup>8,10,18</sup> Although the germ of cereal grains and green leafy vegetables represents the richest natural sources of vitamin E, so universal is its distribution in the plant world that no one has as yet been able to devise a diet of natural foods

suitable for the experimental production of vitamin E deficiency.<sup>7</sup>

A considerable number of animals have been observed to die suddenly while on vitamin E deficient diets.<sup>4</sup> One bovine which died suddenly was followed with serial electrocardiograms that showed gradual and progressive changes. Atrophy and scarring of cardiac muscle fibers were found to appear, along with an increase in the cellular elements. It was concluded that cardiac failure could be produced in cattle by means of a vitamin E deficient diet.

The reports<sup>12,13,15,16</sup> on the use of vitamin E in various types of heart disease with much attendant publicity have stimulated an interest in the possible therapeutic effects of this drug. Although there has been no critical study of the effects of large doses of vitamin E, an increasing number of patients have been seen by the authors in consultation who have been placed on vitamin E by their physicians.

The present study was undertaken in an attempt to evaluate by laboratory tests and clinical examinations the effect of tocopherol therapy in selected types of cardiovascular disease.

**Procedure.** In this study 7 patients with hypertensive vascular disease without cardiac enlargement by Roentgen-ray (Group 1), 7 patients with hypertensive vascular disease and cardiac enlargement by Roentgen-ray (Group 2), and 7 patients with classical and

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relatively stable angina pectoris (Group 3) were selected. The patients were seen usually at monthly intervals over periods of 5 to 20 months.

Each patient was given the benefit of a complete history and physical examination for purposes of classification. Electrocardiograms and 2 meter teleroentgenograms of the chest were taken along with blood plasma tocopherol levels to serve as controls. At each subsequent visit of the patient the pertinent interval history was recorded; a cardiovascular examination was performed; and the above laboratory data were repeated.

Medication in each instance was begun with oral placebos; each patient received initially placebos indistinguishable from the capsules containing tocopherol for 1 month. After 1 month of placebos, the patient was given tocopherol orally for 1 month. These 2 preparations were then alternated for periods of 1 month each throughout the period of observation. Purposely every patient was given the impression that he received the identical medication on each occasion.

During the earlier period of study, tocopherol therapy was begun with a daily dosage of 150 mg. of the mixed tocopherols. Later, tocopherol treatment was initiated at levels of 300 mg. daily of the alpha tocopherol. At subsequent visits the dosage of tocopherol was increased so that during the period of observation 13 patients received a daily dosage of 600 mg.; 2 patients received a daily dosage of 300 mg. of the alpha tocopherol for at least 1 or more months, and for 6 patients the maximum daily dosage was 150 mg. of the mixed tocopherols (See Table 1).

**Results and Discussion.** The results are summarized in Table 1. In every patient, it was found that the blood level could be raised significantly by the oral administration of tocopherol. In 21 instances of patients to whom 150 mg. per day of mixed tocopherols were administered for 1 month there was an average increase of 47% in the blood plasma tocopherol level (mean increase from 1.20 mg. per 100 cc. to 176 mg. per 100 cc., Table 2). There was an increase in the blood plasma tocopherol level in every instance, and the increment was thought to be significant in 20 of these.

In 11 instances of patients who received 300 mg. per day of alpha toco-

pherol for 1 month there was an average increase of 54% in the blood plasma tocopherol level (mean increase from 1.28 mg. per 100 cc. to 1.97 mg. per 100 cc., Table 2). There was a significant increase in 10 instances. There was some question whether the medication was taken in the 11th.

In 23 instances of patients who were given 600 mg. per day of alpha tocopherol for one month there was an average increase of 85% in the blood tocopherol level (mean increase from 1.59 mg. per 100 cc. to 2.95 mg. per 100 cc., Table 2). An increase in blood level was noted in every instance; in 22 the increase was thought to be significant.

In the hypertensive group without cardiac enlargement (Group 1), 2 patients felt generally better during the period of placebo therapy. This improvement was maintained throughout the period of study with alternating tocopherol and placebo therapy without significant change in blood pressure. In 2 patients the T-waves of the electrocardiogram became lower while on tocopherol therapy. One patient felt less well during tocopherol therapy. The remainder of the patients manifested no significant changes.

In the hypertensive group with cardiac enlargement (Group 2) 2 patients improved subjectively on placebo therapy but exhibited no objective changes. This improvement was maintained. Two patients with bundle branch block developed increasing enlargement of the heart; 1 of them progressed to congestive failure. No improvement was noted in the other patients of this group.

Of the 7 patients having angina, (Group 3) only 1 reported an increase in tolerance to exercise which began while receiving tocopherol. This improvement was sustained throughout the period of study. An additional patient improved while on placebos and maintained improvement throughout

TABLE 1.—ANALYSIS OF RESULTS OBTAINED

TABLE 1.—ANALYSIS OF RESULTS OBTAINED														
Case No.	Age	Sex	Mean B.P.	Heart Size by X-ray	Control Electro-cardiogram	Tocopherol Blood Level (mgm. %)	Tocopherol Therapy				Placebo Therapy		Months of Observation	Remarks
							Mean B.P.	Heart Size by X-ray	Electro-cardiogram	Maximum Daily Dosage (mgm.)	Mean Tocopherol Blood Level (mgm. %)	Range of Tocopherol Blood Plasma Levels (mgm. %)		
Group 1. Hypertensive Vascular Disease														
1	46	F	215 115	Upper limits of nor.	Nor.	1.53	233 135	N.C.*	150 mixed	1.84	1.63 - 2.09	220 123	13	Worse symptomatically on tocopherol.
								N.C.*				1.45	10	N.C.1.*
								N.C.*	600 alpha	2.40	2.06 - 2.81	1.07 1.70	13	N.C.1.*
2	51	F	166 114	Nor	Nor	1.59	165 110	N.C.*		1.49	1.19 - 1.91	.89 - 1.17	15	Improvement after placebos maintained throughout.
						.94	196 115	T <sub>1</sub> 2.3. less 600	600 alpha	1.92	1.37 - 2.83	.75 - 1.18	8	N.C.1 <sup>1</sup> *
3	53	F	210 110	Nor	Nor.	.67	169 105	N.C.*	600 alpha		2.44	1.48 - 1.93	11	After 1 mo. of placebos felt best in years. Improvement maintained.
						1.77	163 94	T <sub>1</sub> less	600 alpha	2.66	1.64 - 3.98	1.07 - 1.51	7	N.C.1.*
5	63	M	220 110	Nor.	Left axis deviation	1.19	179 100	N.C.*	600 alpha		2.11	1.47 - 1.55	9	N.C.1.*
6	50	F	210 110	Nor.	Nor.			N.C.*	150 mixed		2.04 - 2.17	205 116	9	Improvement on placebos maintained. Lost 30 pounds on diet.
						1.44	197 116	N.C.*				1.08 - 1.53	6	After 1 mo. of placebos less nervous and stronger Impr. maintained.
Group 2. Hypertensive Vascular Disease with Cardiac Enlargement														
7	41	M	180 112	Upper limits of nor	Nor.			N.C.*	150 mixed			1.22 - 1.26	9	Improvement on placebos maintained.
								N.C.*		1.99	1.86 - 2.02	163 94	9	After 1 mo. of placebos less nervous and stronger Impr. maintained.
8	51	F	190 110	Enlarged vent	left vent	1.32	200 112	N.C.*	150 mixed		1.71	1.54 - 1.86	6	
								L. a. d. v. decreased to nor. limits	150 mixed			1.24 - 1.33	6	
9	54	F	190 110	SL enlarged	Left axis deviation	1.31	155 87	N.C.*			1.84		100	
								No longer 1 a. dev.	150 mixed					
10	40	F	180 112	Enlarged	Borderline left axis deviation	1.37	163 97	N.C.*						

11	77	F	264 116	Enlarged to left	Nor.	1.37	228 117	N.C.*	N.C.*	600 alpha	2 17	1.64 - 3.23	1.24 - 1.66	216 116	11	N.C.I. <sup>x</sup>
12	69	F	192 98	Sl. enlarged	Nor.	1.71	183 94	N.C.*	N.C.*	600 alpha	2.39	1.84 - 3.00	1.43 - 1.97	191 98	20	N.C.I. <sup>x</sup>
13	65	F	222 120	Enlarged to left	Left bundle branch block	1.25	188 103	Increasing branch	N.C.*	600 alpha	2.59	2.07 - 3.10	1.40 - 1.58	184 105	10	N.C.I. <sup>x</sup> Mt. progressive.
14	44	F	180 98	Nor.	Left bundle branch block	.69	161 92	Increasing branch	QRS interval incr. from .14 to .16 seconds	600 alpha	1.46	1.12 - 1.93	.66 - 1.02	162 93	17	Developed congestive heart failure on tocopherol.
Group 3. Angina Pectoris																
15	56	M	180 116	Enlarged	Left axis deviation	1.05	185 120	N.C.*	N.C.*	150 mixed	1.63	1.38 - 1.83	1.18 - 1.39	175 116	9	N.C.I. <sup>x</sup>
16	67	I	196 106	Enlarged	Left axis deviation	1.56	148 84	N.C.*	N.C.*	300 alpha	2.67	--	1.67 - 1.74	130 85	5	After 1 mo. of placebos improved. Lowered bl. pres. and less angina of effort. Impr. maintained on tocopherol.
17	57	M	120 76	Nor.	Long P-R Interval	.99	118 80	N.C.*	N.C.*	300 alpha	1.70	1.46 - 1.95	.93 - 1.19	115 84	6	Decrease in angina of effort during tocopherol therapy.
18	50	M	120 70	Nor.	Nor.	1.16	130 90	N.C.*	N.C.*	600 alpha	2.46	2.42 - 2.50	1.07 - 1.24	115 77	5	Increase in angina of effort during tocopherol therapy.
19	60	M	140 100	Enlarged	Nor.	1.12	160 110	N.C.*	N.C.*	600 alpha	2.76	2.16 - 3.36	1.75 - 1.82	133 90	7	Sense of well-being worse during tocopherol therapy.
20	57	F	170 100	Nor.	Nor.	2.01	175 105	N.C.*	N.C.*	600 alpha	4.56	4.46 - 4.69	2.01 - 2.82	165 100	5	N.C.I. <sup>x</sup>
21	58	I	210 94	Upper limits of normal	Nor.	1.32	218 110	N.C.*	N.C.*	600 alpha	2.66	1.72 - 4.53	1.28 - 1.62	207 92	17	N.C.I. <sup>x</sup>

\*N.C. = No change.

N.C.I. = No clinical improvement.

the follow-up period. One further patient became worse on tocopherol therapy. No change subjectively or objectively was noted in the remainder.

Thus it seems well demonstrated that tocopherol therapy produced no appreciable benefits in this group of patients. There was no significant improvement in symptomatology nor in objective findings. Specifically there was no lowering of the blood pressure, no decrease in heart size by Roentgen-ray, nor improvement in the electrocardiogram. The changes which were recorded indicating improvement in some and progression in others were no more than one might expect in the

natural evolution of their cardiovascular disease. No toxicity from the drug was noted in any patient. There was no correlation between the level of blood plasma tocopherol and the clinical course of the patient. In patients with congestive heart failure we found that the tocopherol blood levels<sup>14</sup> were normal and not reduced.

**Conclusion.** In a series of 21 patients with cardiovascular disease followed from 5 to 20 months, tocopherol therapy was found to produce no appreciable benefit either subjectively or objectively.

The blood level of tocopherol can be significantly raised by the oral administration of the drug.

TABLE 2.—PLASMA TOCOPHEROL LEVELS AT VARIOUS STAGES OF THE STUDY.

No.	After 1 Month of Placebos	2 Months Later After 1 Month of 150 mg of Mixed Tocopherols Daily	3 Months Later After 1 Month on Placebos	After 1 Month of Placebos	2 Months Later After 1 Month of 300 mg of Alpha Tocopherol Daily	3 Months Later After 1 Month on Placebos	After 1 Month of Placebos	2 Months Later After 1 Month of 600 mg of Alpha Tocopherol Daily	3 Months Later After 1 Month on Placebos
1	1.24*	1.64	1.14	1.23	1.54	1.66	1.77	3.00	1.79
2	1.22	2.02	1.26	1.43	2.87	1.77	1.66	3.23	
3	1.08	1.59	1.53	1.28	2.59	1.40	1.40	3.10	1.58
4	1.37	1.84	1.33	.95	1.59	.60	1.53	2.34	1.44
5	1.47	2.11	1.57	1.01	1.91	1.19	1.44	2.81	1.07
6	1.62	1.84	1.72	1.01	1.34	1.19	1.07	2.06	
7	1.25	2.07	1.28	1.00	1.55	.82	.82	2.83	1.02
8	.86	1.32	1.02	1.93	2.30	1.83	1.50	2.66	1.93
9	1.02	1.70	.95	1.67	2.67	1.74	1.43	1.34	1.43
10	.89	1.42	1.01	1.33	1.30		1.43	3.98	1.51
11	.89	1.28	.89	1.19	1.95	.93	1.51	2.92	
12	1.53	2.09	1.45				1.24	2.59	1.07
13	1.00	1.37	.82				1.75	2.16	
14	1.48	2.73	1.50				2.56	4.69	2.82
15	1.09	2.10	1.36				1.42	3.28	1.59
16	1.06	1.81					1.59	2.71	1.62
17	1.39	1.83	1.29				2.71	4.53	1.62
18	1.29	1.38	1.18					3.38	
19	1.47	1.72	1.28				1.79	2.89	1.97
20	1.28	1.73	1.42				1.07	2.42	1.24
21	.99	1.46	1.19				1.24	2.02	
							2.82	4.46	
							1.17	2.19	1.23
Average	1.20	1.76	1.26	1.28	1.97	1.34	1.59	2.95	1.66 Average

\* All figures represent blood plasma tocopherol levels in mg. per 100 cc.

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# ELECTROCARDIOGRAPHIC CHANGES IN ACUTE GONOCOCCAL ARTHRITIS AND MYOCARDITIS SIMULATING ACUTE RHEUMATIC POLYARTHRITIS

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It is well known<sup>4,6,12</sup> that from 60 to 80% of patients with acute rheumatic polyarthritis present diagnostic electrocardiographic changes. Although similar alterations of the electrocardiogram may occur in numerous infectious and other febrile diseases, the absence of polyarthritis in these disorders facilitates the differential diagnosis. Reiter's syndrome of urethritis, conjunctivitis and polyarthritis has lately been noted to affect the electrocardiogram<sup>5</sup>; however, the ocular and genital manifestations and its limitation to the male sex serve to exclude acute rheumatic polyarthritis.

In presenting 4 instances of acute gonococcal polyarthritis with electrocardiographic changes, our purpose is to demonstrate a pertinent exception to the axiom that polyarthritis (the usual form in gonorrheal arthritis) plus an abnormal and unstable electrocardiogram is pathognomonic of acute rheumatic fever. We wish also to call attention again to the subject of acute gonococcal myocarditis.

Clinical Abstract.. CASE 1. A 22-year-old woman, with migrating polyarthritis, continuous fever, leukocytosis, rapid sedimentation rate and electrocardiographic changes in the T waves "typical" of acute rheumatic fever, was treated with salicylates without benefit

for 49 days. Finally, roentgenography revealed a septic arthritis. Sulfathiazol halted the progressive arthritis and fever in 5 days. One month later the electrocardiogram had become normal. The right knee and left ankle joints were permanently ankylosed. Diagnosis: Septic Arthritis, probably Gonococcal, with Gonococcal Myocarditis.

S. W. (P. F. No. 887-957), a married negress, age 22, entered the Los Angeles County Hospital on July 19, 1944, stating that she had been quite well until one week before, when the left little finger began to ache and swell. The next day her left foot began to enlarge and hurt; and a day later the right knee became involved. She denied previous arthritis, chorea, trauma, vaginal discharge, and recent pharyngitis.

Physical examination: Temperature 102°, pulse 110, blood pressure 130/70. The tonsils were large, but did not appear infected. The heart was normal. The left little finger, left ankle, and right knee were swollen, red, hot, very tender, and extraordinarily painful on motion. Because of the obesity (200 lbs.) and arthralgia, pelvic examination was omitted.

Laboratory studies: Hb.—12 gm., RBC—4,530,000, WBC—10,650, with 75% PMN, 1% PME, and 24% L. Wet chamber preparations disclosed no sickling of the erythrocytes. Sedimentation rate, 25 mm. (Wintrobe). An electrocardiogram (Fig. 1-A) the day after entry showed low voltage T<sub>1</sub>, inverted T<sub>2</sub>, T<sub>3</sub> and T<sub>4</sub>F and a PR interval of 0.16 second.

Course: Because of the clinical picture plus the typical electrocardiopathy, a diagnosis of acute rheumatic fever was assumed and 160 grains of sodium salicylate were given daily. Nevertheless, fever and arthritis persisted, and the right knee became markedly swollen.

On August 8 (20th hospital day), a second electrocardiogram (Fig. 1-B) disclosed the PR interval to be 0.20 seconds, with  $T_3$  and  $T_{4F}$  now isoelectric. On the same day, a complement fixation test for gonorrhea was negative; this test plus the abnormal and fluctuating electrocardiograms reinforced the diagnosis of acute rheumatic fever. On August 25 (37th hospital day) fever and arthritis continued; a third electrocardiogram (Fig. 1-C) was similar to the prior tracing; moderate anemia became manifest (Hb—10 gm.; RBC—3,720,000), the leukocyte count was 5,750 and the sedimentation rate was 23 mm.

revealed "narrowing of the joint space with irregular erosion of the femoral condyles, most consistent with a septic arthritis." A serial film one month later showed slight increase in the destruction of the knee joint; at this time, the left ankle and foot presented "bony demineralization of the tarsal and metatarsal bones, consistent with septic arthritis." During this period of normal temperature and improvement by treatment with physiotherapy, an electrocardiogram (Fig. 1-D) taken October 16 (89th hospital day) was entirely normal.

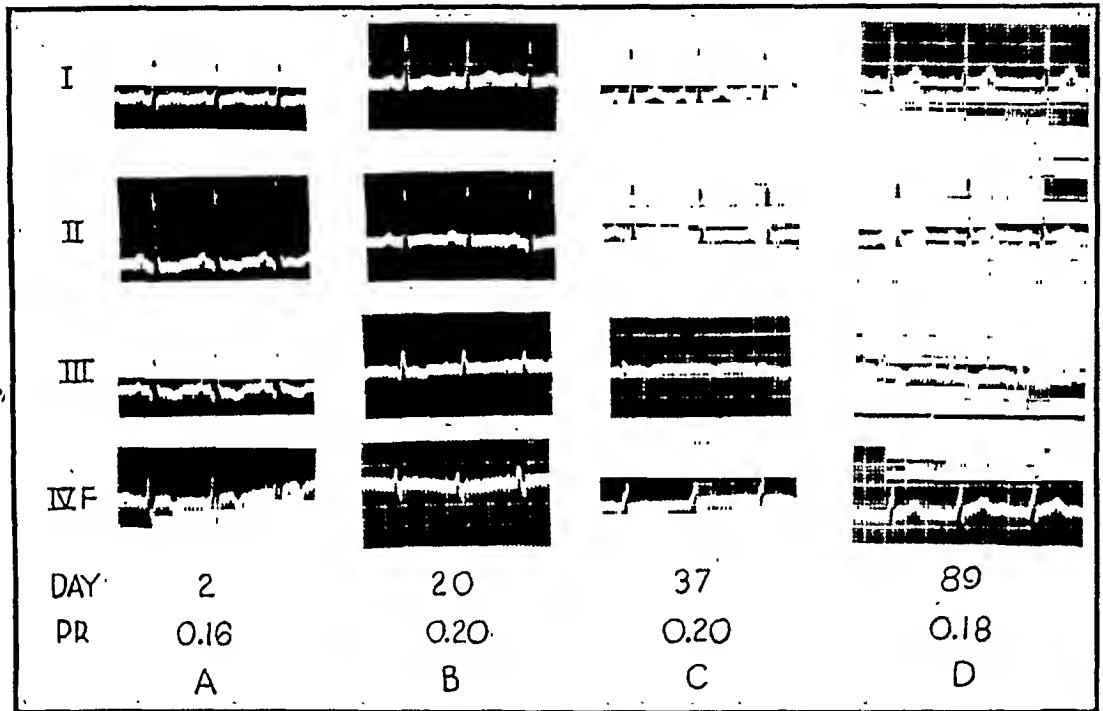


FIG. 1.—Electrocardiograms of Case 1, showing variation in the T waves. A, before treatment. B and C, during salicylate therapy. D, 37 days after sulfathiazol therapy.

Despite no clinical improvement, adequate salicylate therapy was continued for a total of 7 weeks. During this time, the uric acid was 1.1 mg. per 100 cc., a second complement fixation test for gonorrhea was negative, and agglutination tests for undulant fever were negative. On September 9 (52nd hospital day), in the face of a recent spread of the arthritis to the left elbow, salicylates were discontinued and sulfathiazol therapy was instituted; on that day, the leukocytes numbered 10,950, the sedimentation rate was 20 mm., and the hemoglobin had fallen to 8.5 gm. After 5 days of treatment with sulfonamide, the patient became afebrile for the first time in 8 weeks and the pain was greatly relieved. On the 3rd day of this treatment (55th hospital day), roentgenography of the right knee

**CASE 2.** A 19-year-old woman with migrating polyarthritis, continuous fever, leukocytosis, rapid sedimentation rate and electrocardiographic changes in the PR interval and T waves "typical" of acute rheumatic fever was treated without benefit for 57 days. At that time a septic joint was disclosed by the x-ray and urethral and cervical cultures revealed gonococci. Penicillin effected a cure in 7 days. One month later the electrocardiogram had become normal. Permanent ankylosis of the right elbow remained. Diagnosis: Gonococcal Arthritis, with Gonococcal Myocarditis.

O. F. (P. F. No. S17-746), a 19-year-old Mexican housewife, entered the Los Angeles County Hospital on May 29, 1944, complaining of painful swelling of the right elbow and left ankle for 4 days. She denied extramarital



exposure and did not admit sexual contact since her husband's furlough some 4 months prior to entry. There was no history of rheumatic fever or arthritis. Tonsillectomy had been performed 11 years before for frequent sore throats.

**Physical Examination:** Temperature, 101°, pulse 108, blood pressure 104/80. No cardiac murmurs were heard. Pelvic examination disclosed a normal menstrual period in progress. The right elbow and left ankle were very tender, swollen, red and hot.

hospital day), other joints became painful, the sedimentation rate was 46 mm., and the fever was unabated. In an effort to achieve a therapeutic salicylate level, sodium salicylate was given intravenously according to the method of Coburn. Because a chill occurred after 100 cc. had been administered, the treatment was stopped. Since the patient stated that she had been greatly relieved of the painful joints by the intravenous salicylate, another injection was given the next day and a chill again resulted.

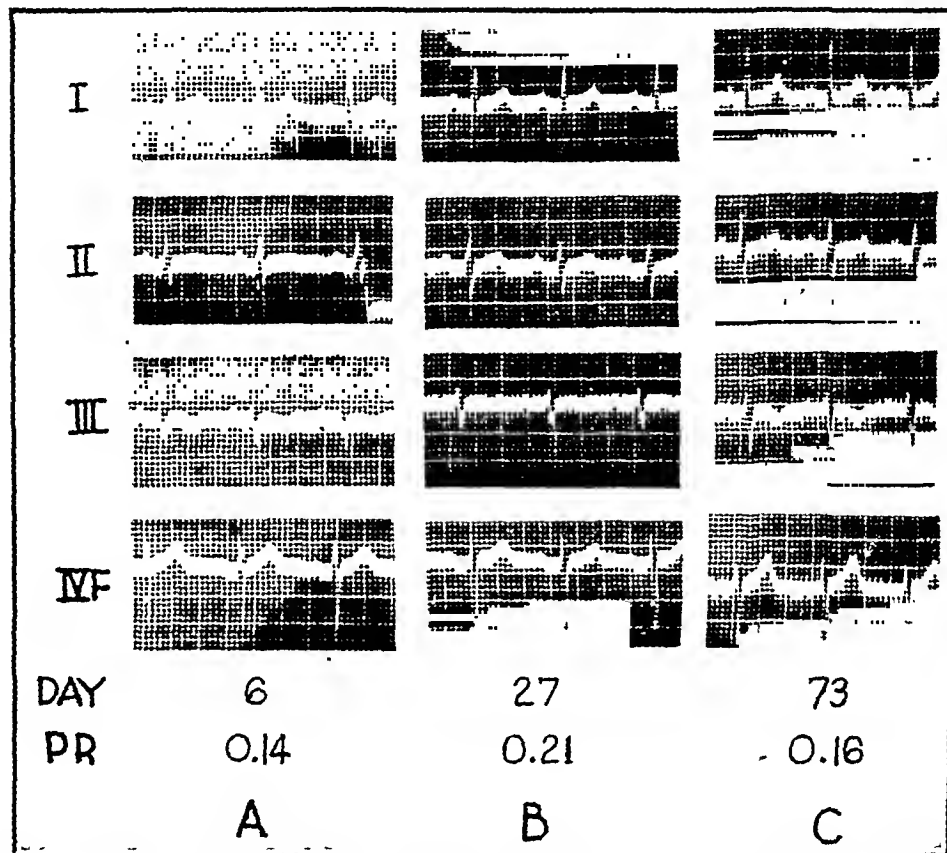


FIG. 2.—Electrocardiograms of Case 2, showing abnormalities of the PR interval and T waves. A and B, during salicylate therapy. C, 16 days after penicillin therapy.

**Course.** On May 29 (2nd hospital day), cervical and urethral smears showed no gonococci. The sedimentation rate was 34 mm. (Wintrobe). A gonococcal complement fixation test was negative. With all the evidence favoring the diagnosis of acute rheumatic polyarthritis, sodium salicylate was started the next day (12 gm. per diem). On June 2 (6th hospital day), an electrocardiogram showed no abnormality; the PR interval was 0.14 seconds (Fig. 2-A). On June 8 (12th

On June 18 (22nd hospital day), the arthritis had progressed despite salicylate given in adequate oral dosage; the right shoulder was very painful and tender. An electrocardiogram taken on June 23 (27th hospital day) revealed the PR interval to be 0.21 seconds, further buttressing the diagnosis of acute rheumatic fever (Fig. 2-B). The salicylate dosage was increased to 15 gm. per day on June 30 (34th hospital day) without benefit. On July 13 (48th hospital day),

repeated cervical and urethral smears were negative for gonococci. Agglutination tests for the specific fevers were negative. A coccidioidin skin test was negative. The blood uric acid concentration was 1.3 mg. per 100 cc. Four blood cultures were sterile.

On July 14 (49th hospital day), roentgenograms of the right elbow disclosed a destructive arthritis. In a few days, urethral and cervical cultures taken at the time of the second negative smears were reported positive for gonococci. On July 22, confronted with this evidence, the patient confessed an extramarital adventure 2 weeks before the arthritis developed. Penicillin, 20,000 units every 3 hours, was immediately administered. After 1 week she was afebrile and the involved joints, although stiff, were painless.

On August 7, (73rd hospital day), after one week of normal temperature, the electrocardiogram returned to normal with a PR interval of 0.16 seconds (Fig. 2-C). She was discharged the next day able to walk, but with the right elbow ankylosed at 165 degrees. She was examined in the orthopedic clinic at intervals; on September 24 she was still complaining of stiffness of the right elbow, pain in the right knee, and stiffness of the left ankle. An x-ray of the right elbow was reported: "Since July 15, the destruction of the articular cartilage has progressed. The bony demineralization has increased." The left ankle showed "diffuse demineralization and narrowing of the talotibial joint."

*CASE 3. A 21 year old woman developed migrating polyarthritis, continuous low grade fever, leukocytosis and rapid sedimentation rate 15 days before a normal delivery took place. Electrocardiographic changes in the PR interval and T waves were "typical" of acute rheumatic fever. Salicylates were given for one week without benefit and were discontinued when septic arthritis was demonstrated radiologically and a positive complement fixation for gonorrhea was obtained. Sulfadiazine arrested the arthritis and effected a cure in 2 days. The electrocardiogram had not returned to normal 17 days later. A permanently ankylosed ankle joint remained. Diagnosis: Gonococcal Arthritis, with Gonococcal Myocarditis.*

S. M. (P. F. No. 895-S17), a Mexican housewife, age 21, entered the obstetrical ward of the Los Angeles County Hospital on September 23, 1944, in the 8th month of her first pregnancy. She stated that she had been well until 3 days before, when she noted swelling of all of her fingers. This was greatly relieved spontaneously, but on the evening before entry the right ankle suddenly became very painful, swollen and hot. There was no

history of frequent or recent sore throats, rheumatic fever, or arthritis.

*Physical examination:* Temperature 99.2°, pulse 100, blood pressure 120/60. The pharynx was normal. No cardiac abnormalities were noted. The uterus was enlarged 22 cm. above the symphysis and fetal heart tones were distinctly heard. The right ankle was swollen, hot, red, tender and was held in plantar flexion. The fingers of the left hand were held in partial flexion and attempted extension was painful.

*Laboratory studies:* Hb.—11.3 gm., WBC—13,800, with 74% PMN and 26% L. Sedimentation rate: 30 mm. (Wintrobe). Electrocardiogram: T<sub>4F</sub> was inverted (Fig. 3-A). On September 25 (2nd hospital day), an x-ray examination of the right ankle disclosed no abnormality.

*Course:* Spontaneous labor occurred on October 5 (12th hospital day) and she was delivered after a short normal labor of a male child. She had no post-partum complaints except for the painful right ankle. On October 11 (17th hospital day), an electrocardiogram revealed a PR interval of 0.26 seconds (Fig. 3-B). Because of the possibility of rheumatic polyarthritis, suggested by the electrocardiographic changes, she was transferred to a medical ward on the 24th hospital (12th post-partum) day. She was re-examined and again no cardiac abnormalities were noted. Fever was seldom above 99°. The finger joints were now entirely normal, but the right ankle showed no improvement. The leukocytes numbered 16,400 with 74% polymorphs. An electrocardiogram (Fig. 3-C) revealed that the inverted T waves in Leads III and IVF had become upright and the PR interval had returned to normal. A third tracing (Fig. 3-D) taken 5 days later (October 23) showed that T<sub>3</sub> was inverted. An orthocardiogram disclosed a heart of normal size and outline. The blood uric acid concentration was 1.4 mg. per 100 cc. An agglutination test for brucellosis was negative. These normal laboratory and roentgenographic results plus the varying electrocardiograms pointed to a diagnosis of acute rheumatic polyarthritis and the next day sodium salicylate therapy was instituted.

A second x-ray examination of the right ankle (after an interval of 30 days) revealed that the tibio-talar joint was narrowed and hazy, being consistent with a septic arthritis. At the same time a complement fixation test for gonorrhea was reported back as positive. On October 27 (34th hospital day) the salicylate was discontinued and sulfadiazine was given with marked relief of the arthralgia within 48 hours. On October 30 (37th hos-

pital day), the sedimentation rate and leukocyte count were normal. An electrocardiogram, however, continued to show changes (Fig. 3-E);  $T_3$  was upright and  $T_4F$  was inverted. On November 8 (45th hospital day), an electrocardiogram (Fig. 3-F) revealed a PR interval of 0.32 seconds. The next day cervical smears were negative for gonococci. An x-ray of the right ankle on November 10 (47th hospital day) showed increased haziness of the tibio-talar joint and further osteoporosis. Clinically, the joint was painless, but ankylosed. On November 13 (51st hospital day) the sedimentation rate was normal, but the electrocardiogram (Fig. 3-G) showed a normal PR interval and lowering of  $T_1$  and  $T_2$ . The patient left the hospital against consent and follow-up has been unsuccessful.

stiffness of the neck and fever of  $102^\circ$  were noted. The next day, both thumbs were very tender; this subsided in 36 hours. Four days before entry, both knees became painful and swollen. There was no prior history of rheumatic fever, frequent pharyngitis or arthritis. For several years, she had had nosebleeds a few days before each period.

*Physical examination:* Temperature  $99.4^\circ$ , pulse 80, blood pressure 110/70. The pharynx was normal. No cardiac abnormalities were noted. Both lower abdominal quadrants were tender. A whitish-yellow vaginal discharge was seen and both adnexal regions were tender. Both knees were markedly tender on their lateral and medial aspects, motion was sharply limited by pain, and the normal surface landmarks were obscured

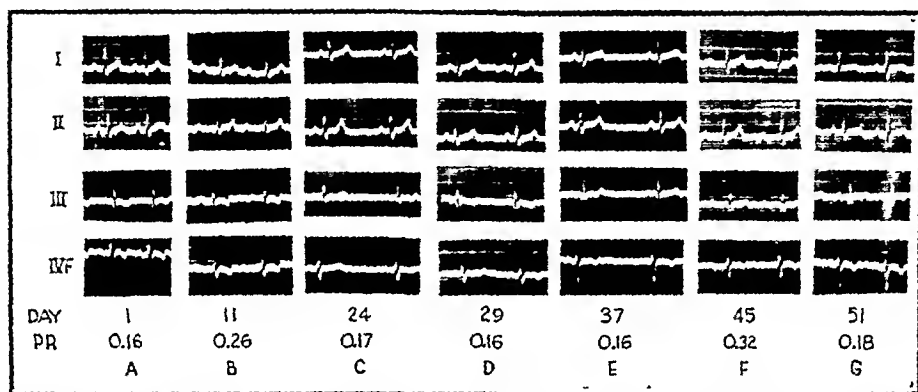


FIG. 3.—Electrocardiograms of Case 3, showing abnormalities of the PR interval and T waves. A, B, C and D, before treatment. E, F and G, after sulfathiazol therapy.

**CASE 4.** A 16 year old girl with migrating polyarthritis, continuous fever, leukocytosis, rapid sedimentation rate and vaginal discharge was treated for presumptive gonorrheal arthritis with penicillin and was cured in 3 days. The complement fixation for gonorrhea was positive. Electrocardiograms, however, revealed changes in the T waves "typical" of acute rheumatic fever. One month later the electrocardiogram was still unstable and abnormal. Diagnosis: Gonococcal Arthritis, therapeutically aborted, and Gonococcal Myocarditis.

C. S. (P.F. No. 936-919), a 16 year old single negress, entered the Los Angeles County Hospital on March 17, 1946, complaining of pain in both knees for 4 days. She had had no abnormal symptoms until a whitish vaginal discharge appeared about one week before entry (and one week after coitus). Shortly after the discharge, burning on urination began. Six days before entry,

by fluid in the joints. Both knees were hot, the right more than the left.

*Laboratory studies:* WBC—11,600. Urethral and cervical smears: no gonococci. Sedimentation rate: 22 mm. (Wintrobe).

*Course:* On the basis of the admitted coitus and vaginal discharge, acute gonorrhea and acute gonococcal arthritis were diagnosed and 20,000 units of penicillin was given intramuscularly every 3 hours beginning on the day of entry. On March 20 (3rd hospital day), an electrocardiogram (Fig. 4-A) revealed isoelectric  $T_1$ , and inverted T waves in the other leads. This might have cast doubt on the diagnosis had not the fever subsided and the arthritis markedly improved. Two days later (5th hospital day) the complement fixation test for gonorrhea was reported positive. Penicillin was discontinued after 5 days; the sedimentation rate was 12 mm. On March 27 (11th hospital day) an electrocardiogram (Fig. 4-B) showed  $T_1$  now

upright and of low voltage. On April 2 (17th hospital day) a roentgenogram of the right knee presented no evidence of septic arthritis. The leukocytes numbered 5,700; the sedimentation rate was 5 mm. She was discharged on the 18th hospital day, the left knee normal, but the right still swollen and tender.

On April 24, 5 weeks after entry, the patient returned to the out-patient department, where the sedimentation rate was 12 mm., and an electrocardiogram (Fig. 4-C) showed QRS<sub>1</sub> now splintered, T<sub>1</sub> and T<sub>2</sub> upright, and T<sub>4</sub>F inverted. She felt well.

was ruled out by the development of a septic joint, the failure of an initial attack of arthritis to respond to salicylates in adequate dosage, and, or, the arrest of the septic arthritis and fever by either a sulfonamide or penicillin. In the first case, the septic arthritis was probably gonorrheal in origin, although 2 complement fixation tests were negative. In the other 3 cases, gonococcal arthritis was diagnosed on

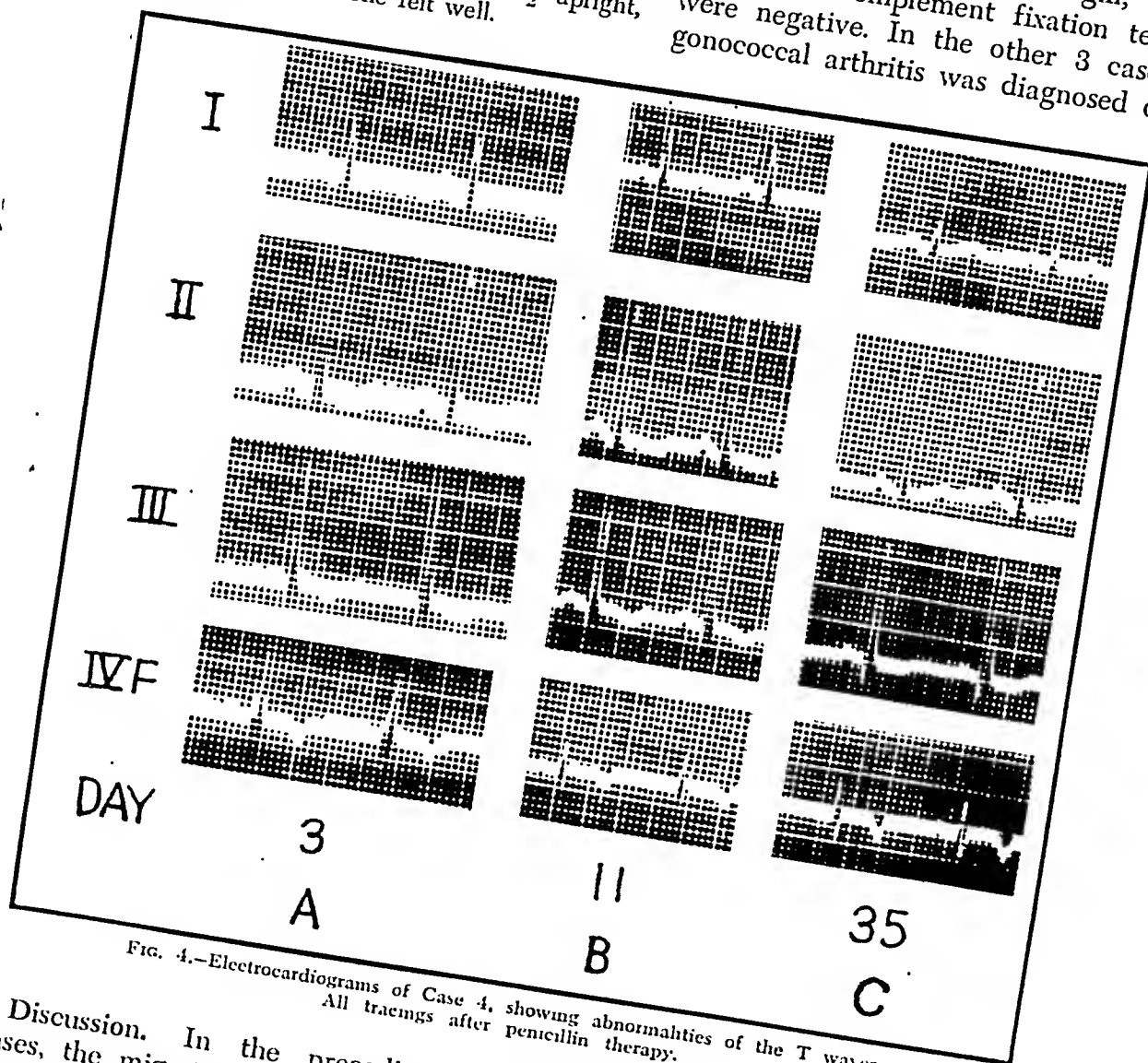


FIG. 4.—Electrocardiograms of Case 4, showing abnormalities of the T waves. All tracings after penicillin therapy.

**Discussion.** In the preceding 4 cases, the migratory polyarthritis, fever, tachycardia, electrocardiographic alterations and increase in sedimentation rate simulate the criteria proposed by Jones<sup>8</sup> for acute rheumatic polyarthritis. Nevertheless, rheumatic fever

the basis of positive cervical cultures or positive complement fixation tests, the radiologic and clinical evidence of septic arthritis, and the prompt halt of the disease by an antibiotic.

Identical electrocardiographic abnormalities in gonococcal arthritis have

been reported by others without the present nosologic emphasis. Master and Jaffe,<sup>10</sup> in 1934, in a study of electrocardiographic evidence of cardiac involvement in acute diseases, described PR and T wave abnormality in 19 cases of gonorrheal arthritis. Gadrat and Morel<sup>17</sup> in 1935 reported from France electrocardiographic alterations in a man with gonorrheal urethritis and arthritis. Ole Bang,<sup>1</sup> of Copenhagen, in 1940 made the electrocardiographic diagnosis of gonorrheal myocarditis on 6 men, 5 of whom were suffering from recurrent specific arthritis and 1 with acute urethritis and arthritis. He found reference in the European and Scandinavian literature to only 3 similar instances. Candel and Wheelock,<sup>3</sup> in 1945, in a study of 11 patients with diverse illnesses complicated by myocarditis as disclosed by electrocardiographic abnormalities, noted 3 instances of gonococcal arthritis with myocarditis.

The cause of the electrocardiographic alterations in these cases is suggested by Katz,<sup>9</sup> who lists the electrocardiographic changes assignable to acute diseases as due to: 1) Inflammatory myocarditis, transient or permanent; 2) Toxic myocarditis ("result of a toxic action on the myocardium presumably due to some by-product of the infecting organism"); 3) Associated pyrexia, which affects particularly rate and ectopic beat; 4) Sympathetic or vagus nerve action on the heart; 5) Relative coronary insufficiency due to anemia, increased metabolic activity of the heart, or both; 6) Vasomotor collapse; 7) Pulmonary emboli; 8) Coronary emboli.

It is our opinion that the electrocardiographic changes were probably caused by so-called "toxic myocarditis", secondary to the gonorrheal infection. In Cases 1 and 2, the electrocardiogram had become normal within one month after the cure of the gonorrhea. In Case 3, the patient left the hos-

pital on the 17th day against consent while the electrocardiogram was still abnormal. In Case 4, despite a very short total illness of only 6 days of both gonorrhea and arthritis before treatment with penicillin was inaugurated, and the fact that a cure was effected in no more than an additional 3 or 4 days, the electrocardiogram was abnormal and variable on the 11th and 39th day after the onset of treatment.

Isolated myocarditis caused by the gonococcus has never been described anatomically. Saphir,<sup>13</sup> in his painstaking study of myocarditis, was unable to verify any instance of isolated gonococcal myocarditis without an associated endocarditis. In fact, the myocardium is assumed to become infected by the gonococcus via direct extension from the diseased valve.

With these considerations in mind, the myocarditis demonstrated electrocardiographically in Cases 1, 3 and 4 reported here must be assumed to be of the toxic rather than the inflammatory type. In Case 2, the electrocardiographic change was limited to variation in the PR interval, and appears to be caused in great part by increased vagal stimulation. A comparable situation is very common in acute rheumatic carditis.<sup>2</sup> In addition to T wave changes mentioned, significant PR interval increases were noted in Cases 1 and 3. In none of these cases was a diastolic murmur, an essential for the diagnosis of gonococcal endocarditis, heard; nor were emboli manifest.

Conclusions. 1. Electrocardiographic changes and polyarthritis can no longer be accepted as pathognomonic of acute rheumatic fever, because:

2. Identical electrocardiographic alterations and polyarthritis can occur in acute gonococcal arthritis.

3. The electrocardiopathy is apparently caused by toxic gonococcal myocarditis, rather than a true inflammatory lesion.

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## AMYLOID HEART DISEASE

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It is the purpose of this communication to bring attention to a small group of patients exhibiting signs of heart disease and intractable heart failure caused by the infiltration of amyloid material into the various structures of the heart. The amyloid disease found in such instances has been designated as primary systemic amyloidosis and differs in several respects from that found in the more common secondary type of amyloidosis associated with chronic suppuration, neoplasm or chronic infections. The major differences between the two styles lie in their different staining reactions to iodine, congo red and methyl violet and their usually distinct organ predilections. The primary type exhibits a marked affinity for smooth and striated musculature, especially that of the myocardium and the tongue, the skin, and blood vessels, whereas the secondary type is characteristically found in the liver, spleen, kidneys, and adrenals. It is the almost universal affinity of the primary type of amyloidosis for cardiac muscle tissue that accounts for the commonly observed cardiac signs and symptoms in this disease. In a recent excellent and complete review of the literature on primary systemic amyloidosis Lindsay<sup>1</sup> reported evidence of cardiac amyloidosis in 39 of 43 autopsied cases. Of a total of 48 reported cases of primary amyloidosis studied by Eisen,<sup>2</sup> 26 (54%) exhibited evidences of clinical congestive heart failure directly related to the infiltration of the heart by amyloid material. Myocardial failure in this disease was usually the result of a widespread intersti-

tial deposition of this foreign amyloid material with consequent stenosis or complete obliteration of the venules and capillaries of the myocardium leading, in many instances, to fibril atrophy and, or, necrosis. Other contributing causes for the myocardial failure were: (a) mechanical interference with the function of the valves caused by the deposition of amyloid in the valvular apparatus, at times giving the clinical picture of organic valvular disease identical with rheumatic heart disease; (b) obliterative infiltration into the walls of the coronary arteries and arterioles and consequent chronic coronary insufficiency; (c) obliterative infiltration into the walls of the pulmonary vessels and alveolar walls with the production of a chronic cor pulmonale; and (d) more rarely, pericardial or endocardial deposits followed by interference of cardiac function.

A report<sup>3</sup> of 3 cases of atypical amyloid disease from Montefiore Hospital in 1935 included 1 case of amyloid heart disease with marked congestive heart failure. Within the last 5 years there have come to autopsy at Montefiore Hospital 2 additional instances of this rare disease, each presenting the picture of intractable congestive heart failure. Clinical and autopsy reports of these cases follow:

**Case Reports.** CASE 1 (E.P., Hist. No. 35812): A 47 year old white male house painter was admitted on April 13, and died on April 22, 1943. He had been in good health until 16 months before admission when he developed a moderately severe upper respiratory tract infection with low grade fever lasting for 1 week. In July 1942, he noted for the first time shortness of breath on climb-

ing stairs and swelling of both legs. These symptoms were thereafter constant, progressive and were soon associated with serotale edema, classic exertional angina, and a severe cough with scanty expectoration which was occasionally blood streaked. In August 1942 he was admitted to Mount Sinai Hospital because of these symptoms. There he responded favorably to the routine cardiac regime of bed weeks, despite routine cardiac therapy and a right thoracentesis directed towards the relief of congestive heart failure. Two months later, in February 1943, he re-entered Mt. Sinai Hospital in a state of advanced congestive heart failure which showed practically no response to vigorous therapy. The massive anasarca persisted and the right hydrothorax refilled in spite of numerous thora-



FIG. 1.—Myocardium of the left ventricle. Case 2.—S. L.; Autopsy, 10,576. (x 210). Note the diffuse, wide infiltration of amyloid material between the myofibers. The myofibers are atrophic and degenerated.

rest, digitalization and mereurialization and was discharged to the clinic on maintenance therapy. At Mt. Sinai Hospital, his heart was found enlarged to the left both on clinical and fluoroscopic examination, with a right axis deviation in the electrocardiogram and no audible murmurs. The cause of the heart failure was uncertain, and suggestions of an occult mitral stenosis or right heart failure due to repeated pulmonary emboli were entertained. In December 1942 he entered Bellevue Hospital with the same complaints, and was discharged unimproved after 2

centeses. His blood pressure was 126/80 and an electrocardiogram was interpreted as indicative of myocardial damage due to an old anterior wall myocardial infarction. Laboratory data collected at Bellevue and Mt. Sinai hospitals showed a venous pressure ranging between 22 and 25 cm. of water, right axis deviation, prolonged P-R interval, sedimentation rate of 20 mm. in 1 hour, total blood protein of 6.7 (3.7-3.0) and 6 gm.  $\gamma$ , negative cephalin flocculation test, normal blood count, cholesterol 200 mg. per 100 cc., a kymographic record showing ample pulsations of



the myocardium with no evidence of pericardial fluid, and urine of high concentration showing 1 to 2 plus albumin, a few wbc clumps, an occasional granular cast and an occasional red blood cell. He was transferred to Montefiore Hospital on April 13, 1943, with the diagnosis of chronic interstitial myocarditis, etiology unknown. The past history and family history were negative.

On admission to Montefiore Hospital, the patient was a fairly well developed, tall, 47 year old white male appearing chronically but not acutely ill. The pupils and ocular fundi were completely normal. The tongue was not enlarged nor grossly abnormal. The cervical veins were distended and filled from below. Coarse moist rales were audible above the level of a bilateral hydrothorax extending over both bases of the lungs. The point of maximum cardiac impulse was visible and palpable in the 5th intercostal space near the anterior axillary line. The heart sounds were of good quality, with a distinct gallop rhythm audible at the apex. The rhythm was otherwise regular at 80 beats per minute. P2 was louder than A2. The blood pressure in the right arm was 112/72 mm. of mercury, in the left arm 110/64 mm. There were no thrills nor murmurs. The liver was firm, smooth and its edge extended 4 inches below the costal margin. The spleen and kidneys were not palpable. Edema of the external genitalia was quite marked. The prostate was slightly enlarged symmetrically. There was massive anasarca involving the lower limbs up to the groin and extending on to the sacrum and up to the anterior chest wall. There was no cyanosis nor clubbing of the fingers or toes. Neurological examination was not remarkable.

**Laboratory findings:** Urine: maximum sp. gr. 1.015 after a concentration test, 1 to 3 plus albumin, and an occasional hyaline and granular cast. The red blood cell count was 4.7 million, hemoglobin 90%, white blood cell count 6800 (67% polymorphonuclear cells, 26 lymphocytes, 5 monocytes, 1 eosinophils, 1 basophils). Serological tests were negative. The fasting blood sugar was 93 mg. per 100 cc. The blood urea nitrogen was 32 mg. per 100 cc. The venous pressure was 20 cm. of water. Circulation time was 29 seconds (ether method), 53 secs. (saccharine). The electrocardiogram showed low voltage, prolonged P-R interval, right axis deviation with right ventricular strain, diminished R4, flat T1, T2, inverted T3, elevated T4. Cardiac fluoroscopy revealed a marked enlargement of the heart transversely with principal enlargement of the left ventricle. Also noted was a bilateral hydrothorax.

The patient's temperature in the hospital was always normal. In spite of vigorous dehydration therapy the patient gained 5 kg. in 9 days. Symptoms were constant and progressive. He was found dead in bed on April 22, 1943, 9 days after admission. The clinical diagnosis was chronic heart failure of unknown etiology, possibly chronic infectious myocarditis.

**AUTOPSY.** (No. 9510 by Dr. Mae Sherman, 10 hours post-mortem): The heart weighed 540 gm. The pericardial surfaces were smooth and glistening and the sac was free of excess fluid. All chambers were markedly dilated and hypertrophied. Friable thrombotic material was adherent to the endocardium of the right atrium and, to a lesser degree, the left atrium. The myocardium was everywhere rather rigid, glistening, pale tannish-yellow, waxy and homogeneous. It measured 16 mm. in thickness in the left ventricle and 5 mm. in the right ventricle. No scars were seen. The muscle gave a positive amyloid stain after the topical application of Lugol's solution. The valves were grossly normal. The coronary arteries were patent throughout with rare small atheromatous plaques. The aorta was likewise grossly normal with the exception of a rare and very small atheromatous plaque. The venae cavae were normal. On histologic examination, the myocardium showed a uniform picture of a very diffuse interstitial infiltration by a pale staining material which separated the myofibers. Most of the myofibers were atrophic or degenerative and were surrounded by greatly thickened sarcolemma sheaths which took a bluish stain. Wide bands and nodules of amyloid tissue separated the atrophic myofibers. The coronary vessels showed no histopathological changes.

The aorta and main pulmonary artery showed considerably and uniformly thickened walls rich in a homogeneous blue staining amyloid material lying between the muscle fibers.

The lungs showed chronic passive congestion, basal atelectases and a bilateral hydrothorax. The small and large pulmonary arteries were moderately thickened and exhibited an occasional small intimal plaque. A medium sized artery in the left lower lobe was incompletely occluded by an adherent embolus. The tracheobronchial lymph nodes were anthracotic and succulent. Histologically, the lungs exhibited signs of chronic passive congestion. There was no amyloid in the bronchial lymph nodes.

The liver weighed 1640 gm. and showed gross and microscopic evidences of chronic passive congestion and early cirrhosis. The

organ was soft, gave a negative reaction for amyloid with Lugol's solution and there was no amyloid material noted on histological examination.

The *spleen* weighed 190 gm., was extremely firm, tense and purplish-grey. The sectioned surfaces and microscopic examination showed chronic passive congestion and an old healed infarct at the lower pole. The tissue failed to take the Lugol stain for amyloid and no amyloid was found on histological examination.

The right *kidney* weighed 180 gm.; the left 220 gm. They were firm, turgid and exhibited several irregular old cortical scars measuring up to 1 cm. in diameter. The sectioned surfaces and microscopic examination revealed passive congestion but were otherwise normal. The tissue failed to take the Lugol stain for amyloid. The *urinary bladder* and the *prostate gland* were essentially normal.

The *pancreas*, *adrenals* and *gastro-intestinal tract* were normal except for congestion. Microscopically, the walls of the submucosal arteries in the intestines showed amyloid infiltrations.

The *bone marrow* contained normal bright red marrow. There were no myeloma cells nor any other abnormality.

The neck organs were not removed.

**AUTOPSY DIAGNOSIS:** Primary amyloidosis of the heart, aorta and pulmonary artery; dilatation and hypertrophy of all chambers of the heart; mural atrial thrombi; chronic passive congestion of the viscera; cardiac cirrhosis of the liver; hydrothorax; ascites; anasarca.

**CASE 2 (S.L., Hist. No. 40742):** A 46 year old white female machine operator was admitted to Montefiore Hospital on June 23, 1946, and died on July 18. She had had frequent physical examinations and was always well until 4 weeks ago when she developed a watery, non-bloody diarrhea, occurring about 15 times a day and associated with abdominal cramps. She recovered in 9 days on symptomatic therapy at Beth Israel Hospital. She returned to work and was free from symptoms except for progressive weakness and fatigability which caused her to cease working several months later. For these latter symptoms she received several injections directed towards correction of an anemia as diagnosed by her local physician. In January 1946 she was treated at Beth-El Hospital for bronchial pneumonia with sulfa drugs and penicillin. During this illness she developed an attack of acute epigastric pain which was diagnosed as biliary colic and confirmed by a cholecystogram. In March 1946 she was readmitted to the Beth-El Hospital for weakness and right upper quadrant pain. She also

complained of recent substernal distress, shortness of breath on effort, orthopnea, and paroxysmal cough. Examination at that time revealed a "somewhat enlarged heart with a systolic murmur of the apex", rales at both lung bases, especially the left, and a tender enlarged liver extending 4 cm. below the costal margin. A roentgenogram of the chest showed an "enlarged mitral type heart" and pulmonary congestion. A gastro-intestinal Roentgen-ray series was negative. A moderate hypochromic anemia with normal leukocyte and platelet counts were reported. A 3-plus cephalin flocculation test, a total protein of 5.9 gm. % (3.1/2.8) and normal routine blood chemical study were also reported. She was discharged with a diagnosis of cardiac decompensation and bilateral bronchopneumonia. Two weeks after discharge from Beth-El Hospital she entered the Hospital for Joint Diseases in a state of chronic, moderately advanced congestive heart failure. As this did not respond to digitalis, mercurials, diet and numerous thoracenteses, she was transferred to Montefiore Hospital on June 23, 1946.

On admission to Montefiore Hospital the patient was acutely and chronically ill with obvious respiratory embarrassment. The pupils, ocular fundi, and tongue showed no abnormalities. The neck veins were distended and filled from below. The point of maximum cardiac impulse was on the 6th intercostal space outside the mid clavicular line. The heart sounds were of poor quality. A short blowing systolic murmur, a reduplicated second sound and a short, early diastolic blow were audible at the apex. This diastolic murmur was not audible to all observers. P2 was accentuated and louder than A2. The rhythm was regular at 80 per minute. The blood pressure was 115/70 mm. Hg. A bilateral hydrothorax was more marked on the left. The abdomen was moderately distended by ascitic fluid and a firm, smooth liver which extended to the umbilicus. The spleen was hard, tender and extended 3 fingers below the costal margin. A 2-plus pitting edema of the lower limbs and the sacrum was evident. The neurological examination was not remarkable.

**Laboratory findings:** Urinalysis: a faint trace of protein, a rare granular cast and a few white blood cells. A complete blood count was normal. The hematocrit was 43%. The blood urea nitrogen was 17.3 mg. per 100 cc. The blood glucose level 83 mg. per 100 cc. The serum albumin was 4.7 gm. %; the serum globulin 1.5 gm. The blood sedimentation rate was 14 mm. in 1 hour. The cephalin flocculation test was negative. The

thymol turbidity was 1 unit. The venous pressure was 17 cm. of water, rising to 18 cm. on liver pressure. The saccharine time 26 seconds. The congo red test showed 59% removal from the blood in one hour. The electrocardiogram showed low T waves and signs of digitalis effect. Roentgenograms of the chest showed a generally enlarged heart, enlarged left atrium and fluid at both lung bases.

The course in the hospital was progressively downhill in spite of diet, bed rest, oxygen, digitalis and mercurials. The patient died suddenly on July 18, 1946. The clinical diagnosis was chronic rheumatic heart disease with mitral stenosis and insufficiency and congestive heart failure.

**AUTOPSY** (No. 10,576 performed by Dr. Alfred Baer 7 hours post-mortem): The neck organs, tongue, larynx, thyroid, and parathyroids were grossly normal. On microscopic examination, amyloid deposits were found in the sarcolemma sheaths of the muscle fibers of the tongue, the walls of the small lingual blood vessels, the basement membrane of the epithelium of the vocal cords of the larynx, and in the interstitial connective tissue of the thyroid gland.

The heart weighed 460 gm. The pericardial surfaces were everywhere smooth and glistening with no excess fluid. The myocardium measured 14 mm. in thickness in the left ventricle and 7 mm. in the right ventricle. It was peculiarly firm and was pale tannish brown and waxy. The mural endocardium and the tricuspid, pulmonary and aortic valves were smooth and glistening. The mitral valve was thickened in its distal portion and presented a thin ridge of fine pinkish-grey nodules along the line of closure. The mitral orifice admitted two fingers freely. The chordae tendinae were normal. All chambers of the heart were dilated and their walls slightly thickened. The coronary ostia and arteries were everywhere widely patent and thin walled. The aorta was smooth, elastic and thin walled. On histologic examination, large areas of the myocardium of both ventricles and atria were replaced by masses of amyloid material. On cross section, the myofibers were frequently surrounded by wide rings of amyloid tissue. The myofibers were often fragmented, granular and focally atrophic. The endocardium of all chambers was extensively infiltrated with amyloid in streaked and mass formations. The intermuscular arteries exhibited amyloid deposits in their walls but the larger subepicardial arteries were normal. The mitral valve contained patches of collagenous fibers lying adjacent to numerous amyloid deposits. There

was no evidence of rheumatic valvulitis. The tricuspid and pulmonary valves also showed amyloid deposits as did the aorta within its intimal coat.

The lungs were essentially normal except for the presence of amyloid deposits in the walls of the intra-pulmonary arteries. The main pulmonary artery showed similar deposits in the media and intima with compression atrophy of its muscle fibers.

The liver weighed 1800 gm., was firm, waxy, pale brown with a slight pinkish tint (congo red test had been done 1 week previously). Histologically, there was marked amyloid infiltration with compression atrophy of the liver cords.

The spleen weighed 650 gm., was very firm, waxy yet friable when cut. Numerous pinhead sized foci with some confluence were noted on the cut surface. Histologically, there were extreme amyloid deposits almost completely replacing the corpuscles and pulp.

The pancreas was grossly normal but on histologic examination showed amyloid deposits throughout the connective tissue, in places compressing the acinar tissue. Amyloid was also noted in the blood vessels but the ducts were normal.

The right adrenal weighed 8 gm., the left 7 gm. They were fairly firm and had a wide, bright yellow cortex. Histologically extensive amyloid deposits were found in the zona fasciculata with resultant compression atrophy of the cortical cells.

The entire gastro-intestinal tract was free from gross abnormality but amyloid deposits were seen throughout the blood vessels and frequently within the mucosal and muscular coats.

The right kidney weighed 150 gm.; the left 140 gm. They were soft, flabby and congested. The urinary bladder exhibited a congested mucosa. The Fallopian tubes, ovaries and corpus uteri were absent. The vagina was atrophic. Histologically, the renal parenchyma showed no amyloid material but the arterioles were heavily infiltrated.

The rectus abdominis muscle was pale but otherwise normal on gross inspection. Amyloid was absent on histologic examination.

The brain weighed 1400 gm. The pituitary weighed 500 mg. Grossly, there were no abnormalities. Amyloid material was found histologically in its vessels.

A strongly positive Lugol test for amyloidosis was found in the liver, spleen, myocardium and endocardium. Weakly positive tests were noted in the kidney, thyroid, adrenal cortex, pulmonary arteries, aorta, pancreas, breast, mesenteric lymph node, esophagus, colon, stomach and small intestine. A

very faintly positive test was found in the tongue and striated skeletal muscle. Congo red stains were done on all tissue sections and the amyloid everywhere failed to take the usual salmon pink color. Instead, it appeared orange and was hard to differentiate from the stain of normal tissue.

**Comment.** The number of cases of primary systemic amyloidosis that we could find reported is indeed small; the correct antemortem diagnosis has been made in only 8 of the 46 autopsied cases. Yet a careful study by Eisen<sup>2</sup> of the reported cases revealed a fairly definite clinical pattern characterized chiefly by a high incidence of congestive heart failure (54%), macroglossia (42%) asthenia (42%) and weight loss (31%). It is this picture of congestive heart failure with or without macroglossia which sharply differentiates the disease clinically from the secondary type of amyloidosis. Clinical findings and tinctorial characteristics similar to those of primary amyloidosis are found, at times, in the amyloid disease associated with multiple myeloma, but these may be differentiated from the primary type by the classic hyperglobulinemia and plasma cell invasion of bone in multiple myeloma.

The 2 cases described above are reported in order to bring attention to this small group of patients presenting signs of intractable congestive heart failure of unknown etiology. These patients usually show enlarged hearts without evidences of valvular disease, hypertension or coronary sclerosis. Electrocardiographic changes are frequently interpreted as showing myocardial damage in the form of altered

T waves, prolonged P-R intervals and low voltage. The most characteristic clinical feature of this type of heart disease is the intractable type of congestive heart failure and a very rapid downhill course in spite of vigorous therapy. As Soma Weiss<sup>6</sup> stated, "without a critical attitude, one is likely to conclude that these patients are suffering from the common diseases of the heart and aorta". The clinical diagnosis is difficult but may be established by the demonstration of amyloid material with bizarre tinctorial reaction in biopsies from the tongue or other skeletal muscle, buccal mucosa or skin. The establishment of a correct clinical diagnosis in such cases could perhaps offer the opportunity for the study of various therapeutic agents such as crude liver extract which has been reported as successful, at times, in the therapy of secondary amyloidosis.<sup>3</sup> Certain strains of inbred mice which develop a spontaneous type of amyloidosis<sup>1</sup> resembling in its distribution the primary amyloidosis of humans may offer an excellent experimental therapeutic approach to those interested.

**Summary.** Attention is directed to the syndrome of intractable congestive heart failure produced by the deposition of amyloid material in the heart. Two cases of this unusual condition with autopsy are reported. The hope is expressed that a correct antemortem diagnosis may be made in similar cases by a more critical diagnostic approach to those patients with heart failure who present bizarre clinical features which do not fit into the common diseases of the heart.

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# THE PNEUMONIA OF MEASLES

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IN the past decade the course and prognosis of many of the bacterial diseases has been greatly altered by the application of efficient antibiotic substances. Although no specific agents are available for the treatment of most of the viral infections, the natural history of many of them has been greatly changed because of the effectiveness of chemotherapy in combatting the secondary bacterial complications which often produced a fatal outcome in an otherwise relatively benign disease. It is with one of the bacterial complications of a common viral disease, bronchopneumonia occurring in the course of rubeola, that this paper concerns itself.

Measles is one of the commonest of the acute infectious diseases which affects children, and very few individuals reach adulthood without having had it; Rosenau<sup>5</sup> estimated that about 5 million cases occur annually in the United States. Although uncomplicated rubeola may produce severe illness, it is not dangerous to life unless one of three complications develops; suppurative otitis media, encephalitis, or bronchopneumonia. It is quite difficult to obtain accurate information concerning the incidence of pneumonia in measles because of the inadequacy of reporting of such pulmonary involvement in those who are not hospitalized. This is borne out by the fact that a larger number of cases of bronchopneumonia is noted in patients in the hospital with measles than in individuals treated at home. Further-

more, the criteria used in making the diagnosis of this pneumonia are often questionable, since abnormal physical and roentgenologic findings are quite common in uncomplicated rubeola. Thus, in 3720 cases of measles studied at the Willard Parker Hospital, bronchopneumonia occurred in 22.6%, while in 10,946 patients in New York City<sup>6</sup>, many of whom were treated at home, it was present in only 6%. The higher incidence for the hospitalized group is, without doubt, influenced by the fact that many cases of measles are referred to a hospital for care only after they have developed a complication such as pneumonitis.

The purpose of the investigation described in this paper was to study the clinical course of the bronchopneumonia which occurs in rubeola, to establish definite diagnostic criteria for it, to determine, if possible, the bacterial agents involved, and to examine the effects of penicillin treatment.

**Methods.** All of the patients were admitted to the hospital from August, 1946, to August, 1947. Complete physical examinations and studies of the white blood count and urine were carried out at the time of entry and at frequent intervals thereafter. Cultures of the nose and throat were taken on admission and, in most cases, repeated a number of times during the course of treatment. Blood cultures were made if the temperature was 101F or higher rectally. Blood-heart infusion-proteose peptone-yeast medium was used in all of the bacteriological determinations. Roentgenograms of the chest were made on the day of admission or within 24 hours after coming to the hospital and were repeated periodically in many instances. Oxygen was administered to many of the

individuals in whom a diagnosis of bronchopneumonia was made.

Because of the presence of manifestations of respiratory tract involvement in many cases of measles in which a pulmonary complication is not present, the following criteria were used in making a diagnosis of pneumonia; (1) clinical condition of the patient, (2) degree of respiratory difficulty, (3) physical findings in the chest, (4) roentgenologic abnormalities in the lungs, (5) course of the disease, and (6) laboratory findings, including peripheral white blood count and bacterial flora of the nose, throat and blood. The value of each of these factors in helping to establish the diagnosis of bronchopneumonia is discussed below.

Therapy consisted of penicillin in most of the cases and streptomycin in a few, the choice of agent being decided, in most instances, on the basis of the results of bacteriologic studies of the nose, throat, and blood. Penicillin was given in amounts ranging from 15,000 to 25,000 units intramuscularly every 3 hours and streptomycin in a dose of 0.125 gm. every 3 hours by the same route. Treatment was continued until the temperature had been normal for 5 days, since a shorter period of therapy often led to relapse of the pulmonary disease. Penicillin was exhibited to a number of cases in whom an acute bacterial infection of the lungs was suspected but eventually not proved; these are not included in this report.

**Results. SELECTION OF CASES.** The patients discussed below were observed at the Haynes Memorial Hospital between August, 1945, and August, 1946, a year during which there were many cases of measles in the communities served by the hospital. Of the 163 patients with rubeola who were admitted during this time, 41 were believed by the authors to have pneumonia.

The differentiation of pneumonia in the presence of such a disease as measles, which by itself often produces inflammation of the respiratory tract (Kohn and Koiransky<sup>4</sup>), is difficult. Even with the most thorough study, there are instances where it is impossible to decide whether true pneumonia is present or whether the patient has only severe, uncomplicated rubeola. The withholding of specific antibacterial therapy might furnish clear

evidence of infection of the lung in some cases, but such a procedure does not appear to be justified when the suspicion of severe pulmonary involvement due to bacteria is strong, though not completely proved, particularly in young children in whom this disease has a high mortality rate. Because of this difficulty in diagnosis, one or two cases of severe uncomplicated rubeola may have been included and some instances of true pneumonia omitted from this study.

In selecting cases which were thought to have pneumonia, consideration was given to the clinical and laboratory criteria enumerated above. Clear cut Roentgen-ray evidence of pneumonia was present in 21 cases. Three patients had no roentgenographic examinations. The diagnosis of pneumonia in these cases was made for the following reasons: one had cyanosis, leukocytosis of 40,000, many fine crackling rales over both lung fields, and dullness to percussion and bronchial breathing over the right lung base; another showed severe respiratory difficulty, many rales, and a white blood count of 40,000 on admission to the hospital; the third revealed diffuse rales over both sides of the chest, marked respiratory difficulty, and, although the leukocyte count in the peripheral blood was normal, had had a secondary rise in temperature and appeared severely ill at a time when the rash of measles was fading.

In 17 patients who showed Roentgen-ray changes in the lungs consistent with either uncomplicated rubeola or bronchopneumonia, the diagnosis of pneumonia was made on the basis of the presence of respiratory difficulty accompanied by one or more of the following: cyanosis, marked tachypnea, dyspnea, leukocytosis, fever, or abnormal physical findings in the lungs at a time when the mucocutaneous manifestation of measles were subsiding. In 3 cases without increased

white blood counts, cyanosis, or secondary rise in temperature, the severity of the respiratory distress was marked enough to warrant a diagnosis of pneumonia; it is possible, however, that these were merely cases of severe uncomplicated measles.

**INCIDENCE OF PNEUMONIA.** There were 41 cases of "proved" pneumonia in 163 instances of measles, an incidence of 25.1%. This is, without doubt, not the true rate of occurrence of pneumonitis in rubeola because, as has been pointed out above, hospitalized patients are highly selected and are often admitted only after they have developed a complication of the primary viral infection. Many individuals with

**SEX DISTRIBUTION.** There were 76 males and 87 females with measles; 21 of the males and 23 of the females had pneumonia. This slight difference in the incidence of pulmonary involvement during rubeola in this group is not significant.

**AGE INCIDENCE.** The ages of all of the patients with uncomplicated measles and those who developed infection of the lungs is shown in Fig. 1. The bulk of the pneumonias occurred in children 5 years of age or under, and there was none in the group 10 or more years old. These findings substantiate the well-known observation that pulmonary complications during rubeola are common in young children but are rare in

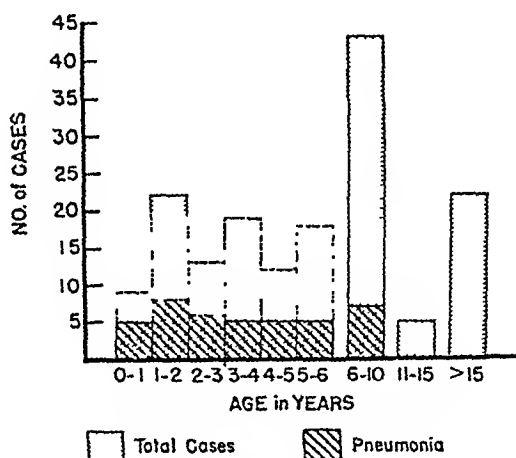


FIG. 1.—Frequency of measles and measles-pneumonia according to age.

mild measles are seen at an infectious disease hospital during an epidemic period, however, because of the necessity of quarantining those who come from boarding schools, colleges, etc., purely as a public health measure. These cases can only counteract, but not cancel, the tendency for patients who are sent to the hospital to be more severely ill than those in the community at large. The incidence of pneumonia in our cases (25%) was substantially the same as that noted at the Willard Parker Hospital (22.6%) some years ago.

adolescents and adults. The number of cases of measles over the age of 15 in this series is probably greater than in the population at large, because, although many had mild illnesses, they had to be quarantined in a hospital because they came from schools, orphanages, and other institutions where proper isolation could not be carried out. Thus, the older patients in this group had rubeola that was generally milder than the average in the epidemic, whereas the younger ones represented some of the most severe cases. Rosenau<sup>7</sup> stated that 50% of measles

occurs under 5, and 97% before 15 years; in the present series, the incidence was 40 and 86% respectively for these two age groups.

**SEASONAL INCIDENCE.** No cases of rubeola were admitted to the hospital in September, October, or November, 1945. The incidence of the disease rose gradually to a peak in April, remained elevated in May and June, and fell during the summer months. The number of patients who developed pneumonia was highest in March and April at the height of the epidemic (Fig. 2). This may have been due either to increased severity of the measles itself or to the greater prevalence of upper respiratory disease at this season of the

patients (14.4%) had had pneumonia from 1 to 3 times prior to developing pulmonary complications during the course of measles. These children, ranged in age from 14 months to 7 years, had first experienced a severe pulmonary infection from birth to the age of 2, and 3 of them had congenital defects; eventration of the diaphragm, spastic paralysis, and mongolism with congenital heart disease.

**TIME OF ONSET OF PNEUMONIA.** The relationship between the probable time of development of pneumonia to the onset of the rash of measles is shown in Fig. 3. Half of the cases in which the rubeola could be dated accurately showed evidence of pneumonitis early

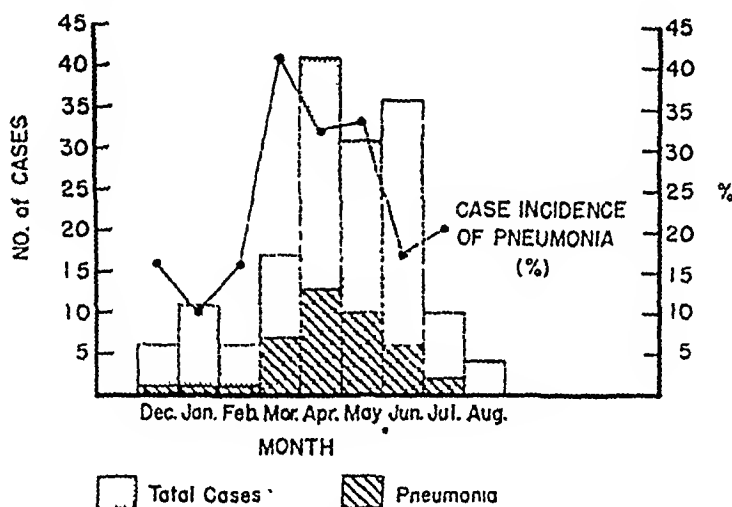


FIG. 2.—Frequency of measles and measles-pneumonia according to season.

year; March and April are the months of peak incidence of scarlet fever in Massachusetts.

**PREDISPOSING FACTORS.** Underlying disease of a serious nature was common in the patients who developed pneumonia during the course of measles. Two individuals were mongolian idiots with clinically evident congenital heart disease. One case showed a spastic paralysis as the result of a birth injury, 2 had "lipoid" nephrosis, 3 manifested severe anemia, and 1 had eventration of the diaphragm and severe obesity.

A history of frequent severe respiratory tract disease was common. Six

in the eruptive stage. In 7, the pulmonary complication occurred only after the exanthem was fading and in a few, it had already disappeared. Five patients had lung involvement before the eruption appeared, 3 during the prodrome, and 2 in the incubation period. The relationship of the measles to the cases of pneumonia which occurred in the incubation period and the one that came on 15 days after the onset of rash may be somewhat questionable.

**PHYSICAL FINDINGS.** The physical findings (other than those in the skin) in patients with pneumonia during rube-



ola are presented in Table 1. One child showed no abnormalities in the lungs by physical examination. Rales, which constituted the change found most often in those with complicating disease of the lungs, were present also with great frequency in uncomplicated measles. Dullness to percussion over various parts of the chest was present in 61% of the cases. Although this sign appeared, at first, to be of great help in making the diagnosis of pneumonia, its usefulness was somewhat impaired by the fact that it was discovered frequently when no pulmonary involvement was present; in addition, the location of the dullness was often on the side opposite to the one in which in-

about half the cases and were found only very rarely in uncomplicated measles. Cyanosis, which occurred in 15% of the patients studied, always indicated the presence of pneumonia.

**TEMPERATURE.** Fever, ranging from 100.8 to 106F (rectally), with a median of 103.2 F, was present in all of the patients at the onset of the pneumonia. In general, the temperature tended to be higher in cases of measles with a pulmonary complication than in those without one, but this finding was of no aid in establishing the diagnosis of pneumonitis in an individual instance. Of considerably greater importance was a secondary rise in temperature after varying degrees of defervescence in the

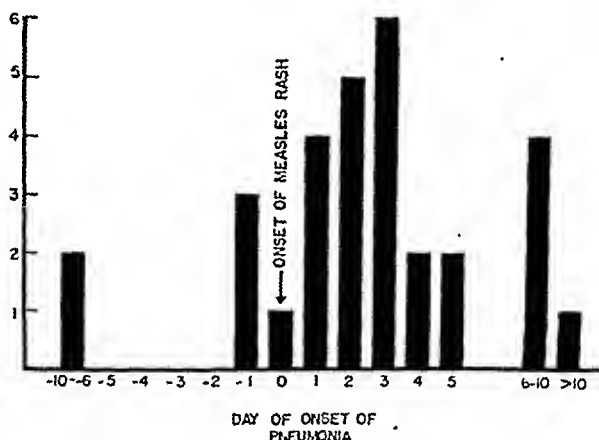


FIG. 3.—Relation between probable time of onset of pneumonia with reference to time of onset of measles.

filtration of the lung parenchyma was demonstrable in the roentgenogram. Bronchovesicular, bronchial and coarse breath sounds were found less constantly and were not reliable indicators of the presence of pneumonia. On the whole, physical examination of the lungs in these patients yielded little information that was useful in making an absolute diagnosis. The presence of a large area of consolidation or a pleural effusion was a much better indication of pneumonitis. Severe dyspnea, flaring of the alae nasi, marked tachypnea, grunting, and retraction of various portions of the chest wall were present in

normal course of the rubeola had occurred.

**ROENTGENOGRAPHIC FINDINGS.** At least one Roentgen-ray examination of the chest was made in all but 3 of the patients; in Table 2 are summarized the Roentgen-ray findings in the other 38 cases. In almost half the group the only abnormality was hilar and peribronchial infiltration. In 13 instances this was interpreted by the roentgenologist as indicative of bronchopneumonia, while in 4 it was thought to be consistent with acute respiratory infection without pulmonary parenchymal involvement. The diagnosis of pneumonia was most dif-

ficult to establish without question in those who exhibited only this type of roentgenographic change. Kohn and Koiransky<sup>3,4</sup> observed similar alterations in the lungs in 40 to 60% of uncomplicated measles. About 60% of these occurred before or during the height of the eruption; infiltration was often present in clinically mild cases,

TABLE 1  
ABNORMAL PHYSICAL FINDINGS ON 41  
PATIENTS WITH PNEUMONIA AND MEASLES

Physical Finding	No. Cases	%
Rales	35	85
Altered Breath Sounds	22	54
Dullness to percussion	25	61
Dyspnea	21	51
Cyanosis	6	15
Fluid (Pleural)	3	7
Distention (Abdominal)	2	5

but was less common in patients less than 1 year of age, and quite unusual in those who had modified rubeola as the result of the administration of immune serum. Six to 10 months later, about 1/3 of the cases revealed pleural thickening; few other residua except occasional localized accentuation of the pulmonary markings were found. The demonstration of pulmonary infiltration by Roentgen-ray examination, therefore, did not make the diagnosis of pneumonia, nor did its absence rule it out. Demonstration of patchy or mottled infiltration, and, or, localized areas of increased density, by Roentgen ray was of much greater help in establishing the likelihood of pneumonia. Abnormalities of this type occurred in 21 of the cases in our series. There was a marked tendency for these to be present on the right side; 3 were in the right upper, 2 in the right middle, and 1 in the right lower lobe; in one instance the exact position of the changes in the right lung was not specified. In only one patient was the area of density found in the left lung: lower lobe. Pleural effusion was demonstrated in only 3 individuals; in 2 it was on the right and in 1 on the left side.

PERIPHERAL WHITE BLOOD COUNT. White blood counts made at the time of admission to the hospital and at fre-

quent intervals thereafter were normal or moderately decreased, with a rise in the number of mononuclear cells, in uncomplicated measles. The number of leukocytes present on admission or at the onset of pneumonia, and the maximum count during the course of the pulmonary disease are presented in Table 3. A rise in the neutrophilic granulocytes in the early stages of the pneumonitis was followed by an increase in the mononuclear cells during convalescence. The total peripheral white blood cell count was elevated in 25 and normal or depressed in 16 patients at the time of admission to the hospital or at the onset of infection of the lungs. Rubeola tends to depress the number of leukocytes, whereas pneumonia, particularly that produced by bacteria, elevates it. In a number of

TABLE 2  
ROENTGENOGRAPHIC FINDINGS IN LUNGS OF 41  
PATIENTS WITH MEASLES AND PNEUMONIA

Type of Change	No.	%
1. Hilar and peribronchial infiltration only	17	45
2. Patchy infiltration	6	16
3. Generalized mottled infiltration	4	10
4. Localized densities with or without 1, 2, or 3.	11	29
5. Density in right upper lobe	3	
6. Density in right middle lobe	2	
7. Density in right lower lobe	1	
8. Density in right lung lobe not specified	1	
9. Effusion—right pleural cavity	2	
10. Effusion—left pleural cavity	1	

the cases reported here, normal counts were replaced by high ones as soon as pulmonary complications developed. Although some of the admission counts listed in Table 3 were not increased, a much better indicator of the true course of events was obtained from a study of the maximum number of white blood cells present during the course of the disease. A single estimation of the white count is not of great significance in establishing a diagnosis of pneumonia; repeated determinations, particularly if a significant elevation occurs and is accompanied by suggestive physical and roentgenographic abnormalities, are of much greater help.

**BACTERIOLOGICAL STUDIES.** Cultures of the nose and throat were made on all patients with measles, without regard to the presence of a pulmonary complication. In many of the cases of pneumonia, bacteriologic examination of the upper respiratory tract was performed at frequent intervals during the entire course of the disease. The sputum

TABLE 3  
WHITE BLOOD COUNTS IN 41 PATIENTS WITH  
PNEUMONIA AND MEASLES

Total WBC	No. of Patients	
	On Admission	Maximum
Less than 5,000	4	....
5,000 — 7,900	4	1
8,000 — 10,900	8	6
11,000 — 13,900	5	6
14,000 — 16,900	8	10
17,000 — 20,900	4	5
21,000 — 25,900	3	4
Greater than 26,000	5	10
Median WBC	13,700	16,300

could not be studied because most of the individuals were young children. Blood cultures were carried out in 21 instances, being repeated several times in some cases. The bacteriological data are summarized in Table 4; the organisms are listed without relation to predominance or the number of times they were present in a single individual. Despite the proved increase in susceptibility to infection with the beta hemolytic *Streptococcus* in measles, this organism was present in only 7 patients. The commonest bacteria recovered were alpha hemolytic streptococci and non-hemolytic *Staphylococcus aureus*. Whether these organisms which are essentially non-pathogenic played a role in the production of the pneumonia in the individuals in whom they were present is difficult to determine. Hemolytic *Staphylococcus aureus* was found in about 25% of the cases. This agent was undoubtedly of great importance since it is known to be a relatively common cause of bronchopneumonia in infants and young children. One of the patients had empyema and another developed bacteremia due to hemolytic *Staphylococcus aureus*. Another organism which was of unquestionable impor-

tance was *Hemophilus influenzae*. It was found in 25% of the cases of pneumonia and produced bacteremia in one individual; this child failed to respond to the administration of penicillin but recovered rapidly after treatment with streptomycin. The other bacteria listed in the table are normal inhabitants of the nose and throat and probably played no role in the production of the pulmonary complications.

**TREATMENT.** All of the cases were given penicillin as soon as evidence of pneumonia was detected, without waiting for the establishment of an etiological diagnosis. As a result of the difficulty in determining definitely the presence of infection of the lungs, about 60% more patients were treated than were finally considered to have this complication. The severity of the symptoms, the high fatality rate of untreated pneumonia in rubeola, and the non-toxicity of penicillin seemed to justify the use of the drug in cases in which the suspicion of pulmonary involvement was strong but a definite diagnosis could not be established promptly. The amounts of penicillin used are discuss-

TABLE 4  
RESULTS OF BACTERIOLOGIC STUDIES OF NOSE AND  
THROAT IN 41 PATIENTS WITH  
PNEUMONIA AND MEASLES

Organism	No. of Cases in Which It Was Found		
	Site of Culture		
	Nose	Throat	Blood
<i>Streptococci</i>			
Alpha hemolytic	10	13	
Beta hemolytic	1	7	
Non-hemolytic	4	6	
<i>Staph. aureus</i>			
Hemolytic	10	9	1
Non-hemolytic	16	20	
<i>H. influenzae</i>	8	11	1
Diphtheroids	6	7	
<i>Micrococcus</i>	1	4	
<i>B. subtilis</i>	1		
<i>P. vulgaris</i>	1		
<i>E. Coli</i>	1	1	
<i>N. Catarrhalis</i>	1	1	

ed under Methods; data concerning the total dose of the drug as well as the varying periods over which it was given are presented in Table 5. The response to penicillin administration was rapid in most patients, with early defervescence and rapid clearing of the abnor-

mal physical findings in the lungs. Fifty per cent of the children had a normal temperature after 48 hours of therapy and only 20% were febrile after 72 hours; fever had disappeared in all instances on the 6th day following institution of treatment (Table 6) except in several of those who had complications of the pneumonia. One patient

TABLE 5

DOSE AND DURATION OF TREATMENT WITH  
PENICILLIN IN 41 PATIENTS WITH  
PNEUMONIA AND MEASLES

Days	No. of Cases	Total dose—Units X1000	No. of Cases
4	2	400 — 599	2
5	8	600 — 799	10
6	5	800 — 999	6
7	3	1000 — 1199	7
8	3	1200 — 1399	4
9	6	1400 — 1599	2
10	3	1600 — 1799	2
11 — 15	7	1800 — 1999	1
16 — 20	300	2000 — 2199	3
20	1	2200 — 2399	2
		2400	2

had a secondary rise in temperature accompanied by an increase in severity of the physical changes in the lungs while receiving penicillin; he was found to have developed a pneumonitis due to *H. influenzae*, type B., probably as a result of a change in the bacterial flora of the nose and throat due to the use of penicillin. Treatment with streptomycin produced a rapid, complete recovery. This case has already been described elsewhere in detail (Weinstein<sup>8</sup>) and will not be discussed again here. The patient with *Staphylococcus aureus* pneumonia and empyema was given penicillin both intramuscularly and into the affected pleural cavity (25,000 units every 24 hours). There were no deaths in the entire group of complicated or uncomplicated pneumonias.

**COMPLICATIONS OF PNEUMONIA.** Complications of the lung involvement in measles occurred in 5 cases. Two patients had bacteremia, one with *Staph. aureus* and the other with *H. influenzae*; the latter was the same one who developed influenza bacillus pneumonia while being treated with penicillin. Pleural effusion was present in 2 in-

stances; in one there was an empyema due to *Staph. aureus* and in the other the fluid in the chest was sterile. Roentgenographic study of the cardiac silhouette of one child showed findings consistent with an effusion into the pericardial sac; the enlargement of the heart shadow decreased gradually. Since the pericardial fluid was not aspirated, it was impossible to ascertain whether it was sterile or contained bacteria. Parenteral penicillin alone, without instillation of the drug into the pericardial sac, produced a complete cure. The *Hemophilus influenzae* pneumonia which developed as a complication of a lung infection due to some other agent has already been mentioned.

**Discussion.** The virus of measles produces a variable degree of respiratory involvement in most cases. Roentgen-ray studies indicate a high incidence of pulmonary infiltration even in mild instances of rubeola. Non-productive cough is one of the most constant clinical features of the disease. Pathologic examination of the lungs of those in whom death has occurred during the course of a non-bacterial pneumonitis complicating measles has revealed mo-

TABLE 6

EFFECT OF PENICILLIN TREATMENT ON TEMPERATURE IN 41 PATIENTS WITH PNEUMONIA AND MEASLES

Temperature	Days of Treatment and No. of Cases					
	0	1	2	3	4	5 6
106 or over	2					
105 — 105.8	5	2	1			1
104 — 104.8	9	2	1	1	1	
103 — 103.8	9	9	6	1	1	1
102 — 102.8	10	6	3	4	2	
101 — 101.8	5	9	8	8	4	3
100 — 100.8	1	9	7	9	7	4 3
100		4	15	23	26	32 36

nonuclear exudate, giant cells (Alkana and Warthin-Finkeldey types), nuclear inclusions in the tracheal, bronchial and alveolar epithelium, and ulceration of the surface of various parts of the respiratory tract due to necrosis of the epithelial cells.

Bacteria are of unquestionable importance in the production of pneumonia in many cases of measles as is

shown by the development of empyema and/or bacteremia due to *Staph. aureus*, *Strep. pyogenes*, or *H. influenzae*. The increased susceptibility of individuals ill with rubeola to infection with the beta-hemolytic *Streptococcus* is too well known to require further comment; in some epidemics, for example the one that occurred in Army camps in 1918, there may be a high incidence of streptococcal pneumonia with empyema. The role of other less pathogenic organisms in this type of pneumonitis is not so well understood but *Strep. viridans* and non-hemolytic *Staphylococci* have been found in the lungs in fatal cases. The part played by bacteria in the production of pneumonia in a particular case of rubeola is difficult to evaluate, even when highly pathogenic organisms are recovered from the nose and throat; they may be present as a result of otitis media, sinusitis, or pharyngitis or may only be normal inhabitants in these sites, as is the situation in healthy carriers. Exact bacteriologic correlation is impossible in most instances because of the inability to obtain sputum in young children; tracheal cultures and puncture of the lung are not practical enough for wide application. The pneumonitis which occurs in measles may be due to the virus itself or to secondary infection with bacteria. The relative role of each of these agents varies from one case to another and is difficult to evaluate in any particular instance unless certain findings are present. A high white blood count with relative increase in the percentage of polymorphonuclear leukocytes, favorable response to penicillin treatment, bacteremia, or the development of a complication such as empyema, pericarditis or bronchiectasis are highly suggestive of bacterial invasion rather than pure viral infection.

Since a varying degree of respiratory tract involvement is present with great frequency in uncomplicated measles, the diagnosis of pneumonia is diffi-

cult to establish definitely in some cases. The application of the following criteria is helpful in reaching a decision concerning the presence or absence of a pulmonary complication: (1) the general clinical condition of the patient, (2) the degree of respiratory difficulty, (3) the chest signs, (4) roentgenograms of the chest, (5) clinical course of the disease, (6) peripheral white blood count, and (7) bacteriologic studies of the nose, throat, sputum, and blood.

The clinical condition of the patient and the degree of respiratory difficulty are of much greater value than the physical findings over the lungs in making a diagnosis of pneumonia in rubeola. Roentgenograms are diagnostic in a little over half of the cases. In instances where physical and Roentgen-ray examination of the chest are of little help, the clinical course of the disease, the peripheral white blood count and bacteriologic studies are often the deciding factors. A secondary rise in fever late in the eruptive stage or failure of the fever to decrease with subsidence of the rash, particularly when accompanied by significant physical and roentgenographic findings, makes more certain the possibility of pneumonia. Increase in severity of the cough, spread of the physical abnormalities in the lungs, or a peripheral white blood count greater than 10,000 with a shift to the left are highly suggestive. The isolation of pathogenic bacteria in large numbers from the nose and throat may also be of aid. When this is the case, however, there is usually other very good evidence of a pulmonary complication; a positive blood culture has much greater significance.

The favorable results obtained in the treatment of the cases of pneumonia reported here with penicillin are very striking. There were no deaths in spite of the severity of the disease in some of the patients. There were only 2 individuals who failed to respond to the usual doses of penicillin: one case of

empyema which was present before any therapy was given and another of *H. influenzae* pneumonia and bacteremia which occurred during therapy; both of these recovered with the exhibition of other forms of treatment. These results are in marked contrast to those obtained at the Willard Parker Hospital<sup>1</sup> and the Kingston Avenue Hospital<sup>2</sup> where the mortality rates were 63 and 14.9% respectively in untreated cases of pneumonia complication measles. In the cases of bronchopneumonia and rubeola treated by Swyer,<sup>7</sup> the incidence of fatalities was 10.3% in those given sulfapyridine and 21% in those not treated. Gibel and Litvak<sup>2</sup> administered sulfathiazole to 53 individuals with the same disease and reduced the deaths to 1.8%.

It is possible that the excellent therapeutic effects obtained in the group described in this paper are due to the inclusion of cases with either no true pulmonary complication or with only very mild pneumonitis. A serious effort was made, however, to apply strictly the criteria discussed above but, even with this, a number of patients were treated who, in retrospect, were finally not thought to have the disease; these are not included in the present report. Comparison of the incidence of pneumonia in our series, (25.1%), with those of the investigators cited above (22.6% at the Willard Parker Hospital, 7% at the Kingston Avenue Hospital and 13.3% in Swyer's group) is impossible because the diagnostic criteria used by them are not described.

Despite a possible variation in the criteria used for diagnosis, the results of penicillin treatment were so favorable as to leave little doubt that it is the agent of choice in the treatment of patients with measles who develop pneumonia. Since the response to this antibiotic agent was so striking in the vast majority of cases, 2 assumptions can be made; (1) a very large number of the pneumonias that occur in rubeola

are either due directly to bacterial infection or are the result of secondary invasion of the lungs by these organisms; (2) most instances of this type of pulmonary involvement are due to Gram-positive bacteria since these are the ones most susceptible to penicillin. The bacteriologic studies of the nose and throat supported this conclusion.

The diagnosis of the pneumonia that complicates measles is difficult to establish with certainty but every effort should be made to evaluate each patient as accurately as possible by the application of the criteria enumerated above. In instances where a decision cannot be reached, the patient is seriously ill, and the suspicion of a pulmonary complication is strong, penicillin should not be withheld, because delay may result in a fatality. On the other hand, the antibiotic should not be used indiscriminately since its use may cause sensitization unnecessarily or, as Weinstein<sup>8</sup> has pointed out, may lead to new pulmonary infections produced by agents insensitive to its action; this is particularly true in individuals suffering from an underlying acute or chronic pulmonary disease. The case of *H. influenzae* pneumonitis and bacteremia described above is an example of this phenomenon.

**Summary and Conclusions.** 1. Pneumonia was found in 25% of 163 cases of measles.

2. Pulmonary complications appeared to be more common in children under the age of 5 than in older individuals.

3. Of the patients studied 50% developed the bronchopneumonia in the early stages of the eruptive phase of rubeola.

4. The definitive diagnosis of serious pulmonary involvement in measles was difficult because of the frequency with which the uncomplicated exanthem is accompanied by physical and roentgenographic abnormalities in the lungs.

5. The application of certain clinical and laboratory criteria was of help in establishing the diagnosis of pneumonia.

6. Most of the serious bronchopneumonias which occurred in the course of

rubeola appeared to be due to Gram-positive bacteria.

7. Penicillin appears to be the agent of choice in the treatment of pneumonia in measles; of a group of 40 patients treated with this drug there was not a single fatality.

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## HOME ACCIDENTS AS A COMMUNITY HEALTH PROBLEM

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WHEN physicians long ago extended their interests from the care of the sick and injured to include prevention as a coordinate activity, the emphasis accorded that concern developed a peculiar imbalance. Prevention evolved as a matter almost wholly related to disease, at first concerned with the communicable diseases, but solidly and progressively advancing to include most of the affairs of the sick. The injured have received much less attention, perhaps because the approach to prevention is less well defined, and partly because accidents and injuries are too commonly regarded as unavoidable, as matters of chance to be endured and patched up but scarcely to be prevented. That attitude is not far removed from the beliefs about disease that were held some centuries ago.

The view gradually gains acceptance that traumatic injuries are preventable, and to a greater extent than many of the diseases having active programs of

control. Neither disease nor injury is to be understood as an evil, a misfortune, bad luck or a mistake of nature, but as the result of a broad biologic law, an expression of life. The answers to why and how accidents have come to be what they are, to behave as they do and to occur in the places they are found, are to be sought in the mass pathology of traumatic injuries as evidenced by modern communities, in other words in the epidemiology of accidents.<sup>21c</sup>

As so often happens with public health problems, the first attention to accidents as a community responsibility centered on the unusual and dramatic misfortunes that affect appreciable groups of people. The catastrophes associated with hurricanes, floods and fire led to establishment of a national organization for disaster relief by the American Red Cross,<sup>41</sup> the first operation having been in the Michigan forest fires of 1881. Again so typically, the original purpose was not prevention but



to afford relief to the victims of these cataclysms. Poisonings of children by lye<sup>21</sup> and the traumatic injuries once so much a part of celebrations of American Independence Day<sup>2a,2c</sup> were natural and early interests of medical organizations. Here the concept of prevention was sharply and forcefully introduced.

As motor cars progressively supplanted horses, a new factor was introduced into the causation of accidents and fast came to rank ahead of most others. The Federal Government took an early interest in the matter through the National Conference on Street and Highway Safety, called by Secretary of Commerce Hoover in 1924. The National Safety Council<sup>7</sup> joined in this through their newly organized Public Safety section. When the frequency of these events reached an all time high in 1936, along with accidents in general, medical organizations joined with others already active to study the situation and to make recommendations. A special committee of the American Medical Association reported in 1939.<sup>2b</sup> The upward surge in numbers of traffic deaths in 1946, following the removal of wartime restrictions on motor travel, caused a renewal of Government interest and the appointment of the President's Highway Safety Conference.<sup>31</sup> What has been accomplished by government and voluntary agencies has led to improvement, but is far from a satisfactory solution of the problem.<sup>29a</sup>

This worth while concern with spectacular and pressing events had by no means left the ordinary affairs unattended, i.e., that large bulk of accidents in the home and at work which constitute the principal cost in accidental deaths and disability. Over the years, American industry<sup>1a,1b,20b</sup> has given so much emphasis to accident prevention<sup>23</sup> as to engender a common opinion that the field is largely limited to occupational injuries. This comes about, not because industry contributes the most

accidents, but because it has done the most about them.<sup>27</sup>

The appreciation that official public health agencies had a responsibility in accident prevention was a matter of slower evolution. Leadership came first from welfare, police and other local governmental authority, from industry, from voluntary agencies such as the National Safety Council<sup>30c</sup> and the Metropolitan Life Insurance Company,<sup>19</sup> and through various agencies of the national government.<sup>29b</sup> The pioneer public health interest in accidents was originally not far from a one man crusade by Earle Brown<sup>13</sup> in Kansas and later in Nassau County, New York. The interest spread. When the Association for State and Territorial Health Authorities met<sup>36</sup> in 1941, the principal attention was to motor accidents but much time was devoted to home and other forms of accidental injury that occur in the normal course of life under peace-time conditions. The American Public Health Association<sup>3b</sup> has since 1942 stressed home accidents as a public health problem. Increasing numbers of state and city health departments have organized divisions for accident control, of which those now existing in Kansas,<sup>2c</sup> in New York state<sup>38</sup> and as proposed for Massachusetts<sup>16</sup> are good examples. A stocktaking of accomplishment and an evaluation of the current situation can be undertaken to advantage. Accordingly, the accidents of civilian populations are here first defined and examined as a community health problem. Home accidents are then presented as the particular concern of medicine and public health.

**ACCIDENTS DEFINED.** An accident is universally understood to be a chance event, developing without foresight or expectation, and resulting in injury, or loss. This broad interpretation must be brought within narrower limits when accidents are considered as a health problem of groups of people, for evi-

dently the episode may relate to a person or a thing, to an injury or a material loss, and may be serious or slight. The first restriction is thus to accidents of sudden traumatic origin that result in physical injury to the person.

A number of practical considerations enter into the limitations to be placed on the seriousness of the effect that follows. To confine attention to fatal accidents is to neglect the losses of time and efficiency<sup>17</sup> that come from temporary disability and permanent physical defect. Economically and socially, these are often more important than death. To account for all of the minor disabilities resulting from inconsequential mishaps is to dissipate effort needlessly, and to divert emphasis from really important matters. Disabling accidents are the significant consideration.

The American National Health Survey of 1936<sup>32</sup> interpreted a disabling accident as any sudden bodily injury that resulted either in disability lasting one week or more, in admission to hospital irrespective of time, or in death. The National Safety Council <sup>30c</sup> considers an accident to be disabling if the effect is prolonged past the day of occurrence. Where concurrent recording is followed the period of two or more days disability is a practical and workable criterion. For survey purposes, where information is collected retrospectively about events within the preceding year, accuracy requires that the period of disability be sufficiently great to be well remembered, hence one week. Each period is individually suited to the purposes to which it is put, but a clear definition is necessary if logical comparisons are to be made.

The stated interpretation of a disabling accident is evidently far broader and more inclusive than the commonly held opinion which limits accidents of community concern to catastrophes, where 5 or more deaths follow a single misadventure, or to what are statistic-

ally classed as cataclysms. A great variety of wholly ordinary affairs of life comes into consideration, and it remains so to arrange them in an orderly classification as to permit satisfactory comparison of the experiences of one community with those of another.

**A CLASSIFICATION OF ACCIDENTS.** The classical procedure for the separation of diseases as they affect individuals is according to the parts of the body primarily affected. The same principle is applied with equal ease to the mass diseases of communities, where disease in such geographical units of population as rural, urban, farm or suburban, forms the counterpart of involvement of the respiratory tract, the circulatory system or other of the great anatomic divisions of the body in the individual person. Specifically, so far as accidents are concerned, the accepted procedure is first to distinguish those mishaps which occur in people's homes from those associated with places of work. All others are classed reasonably enough as public accidents, since they occur in public places, but with one notable exception. Motor accidents in public places are accorded separate recognition because of the numbers involved and the peculiar features associated with the problem. Four great groups of accidents are thus recognized, those that occur in homes, at work, in public places and in association with motor cars.

In order to follow a classification of accidents according to place of occurrence, several arbitrary restrictions must be made. Since home accidents include by definition all mishaps occurring in the home or on the home premises, a limited number of motor vehicle accidents are included, in 1947 about 100. Public accidents include all mishaps in public places, except those associated with motor vehicles. Motor vehicle accidents will be taken to include all that occur in public places, whether asso-

ciated with occupation or not, for the reason that a large proportion of motor cars are used for both business and pleasure and much inexactness results from an attempt to determine in which capacity the car was engaged at the time of the accident. The occupation of a physician is evidently the practice of medicine and scarcely that of operating a car for profit. The motor accident that he has may or may not be in the course of his professional duties. The decision as to occupational use is thus open to a variety of interpretations. Truck operators are evidently in a special category, but the accidents they have occur in public places and are associated with motor cars, in 1947 accounting for about 2,500 fatal accidents. They are included with other motor vehicle accidents. The class of occupational accidents as here considered is best stated as occupational, civilian and non-motor vehicle.

**ACCIDENTS AS A CURRENT HEALTH PROBLEM OF THE UNITED STATES.** Because the effectiveness of prevention depends on specifically directed action, and because that specific action in turn depends on detailed knowledge of the causes of disease or injury, the first objective in the study of a community health problem is to determine its size and its general nature. Recently released vital statistics show that in 1947 some 99,579 deaths in the United States<sup>2c</sup> were the result of accidents, a mortality rate of essentially 69.4 per 100,000 population. The data correspond closely with preliminary estimates of 100,000 deaths by the National Safety Council.<sup>20c</sup>

Civilian accidental deaths when divided into the four categories stated, show 34,500 home accidents (35.0%), 31,700 motor vehicle accidents (32.1%), 18,000 accidents occurring in public places (18.2%) and 14,500 (14.7%) occupational non-motor vehicle accidents. These proportions are for the

United States as a whole. Local conditions and environmental differences lead to appreciable variation, as indicated by the 1947 results for the state of Tennessee,<sup>40</sup> where the distribution was home accidents 34.3%, motor vehicle 36.3%, public 21.3%, occupational 6.2% and other and unknown 2.0%. Motor vehicle accidents exceeded home accidents, the example being selected not because of that circumstance, but principally because the records there are particularly good.

An evaluation of any community or mass disease on the basis of deaths is not the method of choice, for judgment is more satisfactory and informative when the number of events that occur is also available. With accidents and with many of the more important diseases, cases are not officially or uniformly collected and made a matter of record. Deaths are and, as a consequence, the principal interpretation is necessarily made of those data.

The temporary disability associated with a disease condition may be a far more important health consideration than the deaths that occur, as with the common cold. Under other circumstances the proportion of affected persons left with a permanent defect may outweigh the losses from deaths, when the two are viewed on the basis of expected productivity and usefulness during life expectancy.<sup>17</sup> Lacking general and complete information by which to judge the losses from defect and disability, an approximation can be had by local surveys of fatal and non-fatal events. If the surveys are sufficiently extensive and the sample is tested for reliability in respect to the whole, a factor can be derived which will give a reliable index on the basis of known deaths, of the numbers of non-fatal accidents leading to temporary disability, and similarly the number associated with permanent impairment of function.

Thus the National Safety Council<sup>20c</sup> has published estimates for 1947 based

on data from the National Office of Vital Statistics, state industrial commissions, state traffic authorities, state departments of health, insurance companies, industrial establishments and other sources. Of a total of 10,600,000 accidents resulting in death or a disability lasting longer than the day on which the accident occurred, 380,000 caused permanent impairment of function, to include partial and total disability of all grades. Translated into terms of morbidity rates, and using current estimates of population, the approximation of 74 disabling accidents each year per 1,000 population is obtained. Subdivided to give results of disabling accidents in terms of death, defect and disability, the rates per 1,000 inhabitants of the United States, to include both civilian and military populations, are in 1947 respectively 0.7, 2.5 and 71. The more informative expression in terms of man-days lost, as a means of presenting losses from non-fatal accidents, is not possible for accidents as a whole, nor for the specific categories of home, public and motor vehicle accidents, although good information is to be had for various industries.

The direct cost of accidents as judged by death, disability and defect is scarcely representative of the total effect on health, for the financial cost of accidents exerts an important indirect effect through economic pressure, especially when the wage earner or other responsible member of the family is concerned. Estimates of this cost developed by the National Safety Council, despite all the inherent inaccuracies that must attend such appraisals, nevertheless give the almost incredible total of \$7,100,000,000 as the cost of accidents in 1947. This includes wage losses, medical expenses, overhead cost of insurance, property damage, fire loss and indirect costs involved in such things as interference with production and time lost by workers other than the injured.

The favorable record of 1947 in respect to deaths from accidents was attained despite what appears from the simple total of well known events to have been a year with a somewhat greater than usual proportion<sup>39f</sup> of losses from catastrophes. The data are not yet available. These irregular and opportunist occurrences that involve appreciable numbers of people introduce frequency variations comparable to the fluctuations seen in communicable disease and brought about by epidemics. Whether occurring in mass disease or in mass injury, they introduce factors that influence the interpretation of behavior.

The difficulties of the epidemiologist in defining an epidemic of communicable disease are avoided by the statistician through arbitrary decision that a single accident resulting in 5 or more deaths constitutes a catastrophe. The circumstances are variously related to air, water, rail, and motor transportation, to fire, marine, flood and storm, to poisonings, to the accidents of mines and quarries and to events such as earthquakes and explosions. The number of catastrophic deaths<sup>39e</sup> for 1946 has been estimated as 1,074 resulting from 103 accidents, while the 10 year average for 1937 to 1946, was 1,299. The more restricted class of cataclysms, representing deaths from tornado, flood, hurricane and similar disasters, is included in these data. For 1946 such deaths<sup>29b</sup> numbered 148. Three conclusions follow.

The first inference is that these catastrophic, unusual and often terrifying events are but a small factor in determining the totals of those who die from accidents in the United States, since they account for only about 1%. Secondly, the over-all record of 1947, one of the most favorable in all of the years that records have been kept, came despite what appears to be more than the usual contribution by these unusual events. Finally, the deaths and disabil-

ities that result from traumatic accidents are a relatively fixed and regularly recurring health hazard of more or less constant presence. They correspond in their behavior to the endemic pattern of infection that characterizes so many communicable diseases.

**ACCIDENTS AS A WORLD HEALTH PROBLEM.** Differences in classifying deaths due to accident, the varying inclusiveness of reporting, the irregular practices about excluding military accidents and a variety of other factors, make a sound comparison of accident rates between countries impossible. The data of Table 1 are selected from information submitted by 38 countries with the purpose of showing the universal existence of the problem, the range of reported rates and the consistent importance of accidents as a public health problem. Judged by this experience, the United States stands in the upper quartile of countries reporting, with a rate that is exceeded by few countries.

place in 1900 to third in 1946. In 1900 tuberculosis and two other infectious diseases, together with diseases of the heart and nephritis, all caused more deaths than accidents and violence; now in 1946 only cancer and heart disease do so. If accidents are considered alone, 3 diseases are responsible for more deaths.

The military situation is equally informative. Over a long history, disease has been the principal cause of death in armies, even exceeding battle casualties in time of war. Non-battle injuries, the category largely representative of accidental deaths, were a relatively minor consideration. In the European phase of the 1917-1918 and the 1942-1945 wars, the death rates for injuries among American troops were almost identical for the two wars, about 2.3 per 1,000 per annum,<sup>21b</sup> but the relation of injury to disease was completely reversed. Disease caused 9 times more deaths than injury in World War I; in World War II injury exceeded disease

TABLE 1.—DEATHS FROM ACCIDENTS PER 100,000 POPULATION, UNITED STATES AND SELECTED FOREIGN COUNTRIES

Country	Year	Rate
Venezuela	1944	27.5
Portugal	1946	36.1
Belgium	1946	41.1
Sweden	1944	48.1
Switzerland	1944	55.1
Finland	1944	60.8
United States	1946	70.1
Iceland	1940	77.6
Austria	1946	85.3
Egypt	1943	115.8

Source: Statistical Office, United Nations, official reports by countries.

**ACCIDENTS AND DISEASE AS CAUSES OF DEATH.** Existing United States rates for civilian deaths from accident and violence remain numerically at almost the identical level of 1900, 88 per 100,000 population in 1900 and 88 in 1946. The relative position among public health problems is at a higher level<sup>22</sup> since these combined conditions have advanced as a cause of death from sixth

in essentially the same proportion.<sup>21a</sup> This trend was already evident in peace time, for the 1939 death rates for the American Army<sup>15</sup> showed 53% of deaths due to injuries and 43% the result of disease.

**TRENDS IN ACCIDENTAL DEATHS.** A well judged prognosis is as useful in problems of mass disease as with illness

of the individual patient. The outlook is none too happy for any immediate improvement in the accident situation. The gains in death rates since 1900 are not great. For the country as a whole the usual range was from 80 to 90 deaths per 1,000 population in 1900. In recent years it has varied between 70 and 80, and currently is on the borderline of 70. A material improvement got underway shortly before 1920, only to be balanced by the newly introduced factor of the motor car. The increasing numbers of deaths from motor accidents have just about neutralized the gains since made against previously existing

The ten states and the District of Columbia that comprised the United States Registration Area of 1900 (Fig. 1) perhaps serve best in comparing conditions in 1900 with those of 1946, since many variables are eliminated by choice of a uniform area rather than the progressively enlarged territory included within the registration area as time went on. So judged, an improvement has taken place, particularly in recent years and largely through the lesser effect of motor accidents during the war years. It remains to be seen if these gains can be held. To do so will require improved methods and a

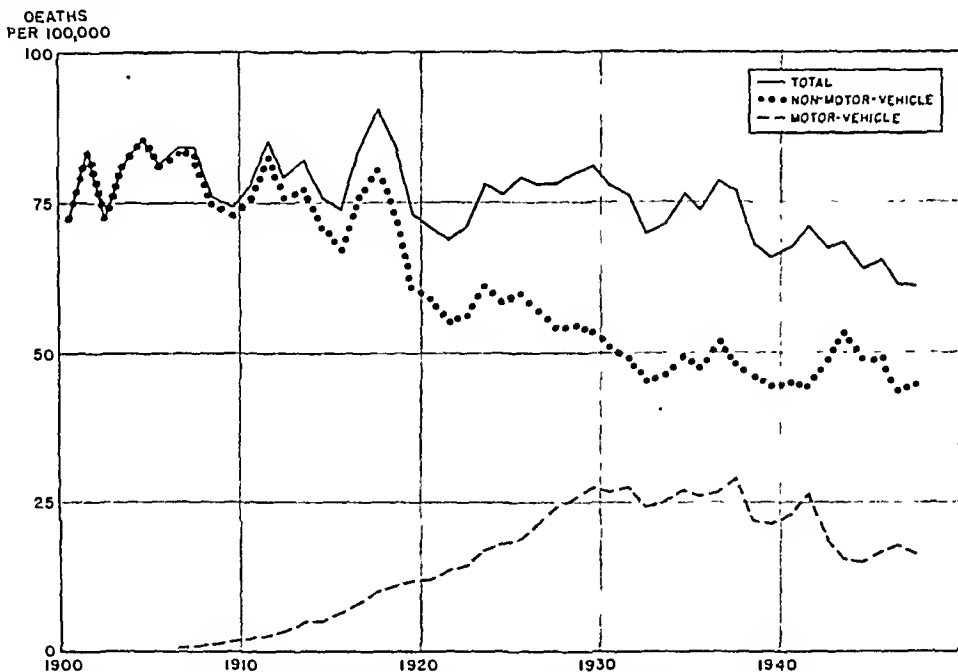


FIG. 1.—Accidents, mortality rates per 100,000 population, states of the United States Registration Area of 1900, 1900-1947<sup>29b,30c</sup>.

conditions. About that same time another factor came into increasing prominence, the aging of the American population. With more people living past 65 years, more were added to the group which consistently has the highest accident rates. This again discounted a potential improvement, and gave further example of how a changing environment, a shift in ecologic equilibrium, acts on health and disease in man.

greater energy in control measures, for the important factor of the motor car assumes increasing weight.

**PATTERNS IN HOME ACCIDENTS.** The accidental injuries that occur in the home are believed to be the particular province of public health and preventive medicine. This implies no conflict with accepted principle, that the maintenance of community health is a community function in which most agencies

of government take part and where a variety of skills is required whatever the problem. The physician regularly has a part, although his activities are reasonably greater in some fields than others.

The main responsibility for the accidents of industry is clearly with the safety engineer, while motor accidents and the diverse mishaps in public places are the special concern of the police and other law enforcement authorities. This may account for the general lack of interest in accident prevention by public health agencies and by private practitioners through preventive medicine. The more likely reason is a failure to dissect the problem; to appreciate that accidents are the fourth cause of death in the United States; and to recognize that wherever they occur and whatever their nature there are many medical considerations. More important still is the inadequate understanding that accidents in the home are numerically the largest class of all; that progress in prevention has been less than with any other accidental injury; and that the only promise for a successful approach seems to be through the facilities and the techniques possessed by health departments<sup>3a</sup> and by practitioners of medicine.<sup>8</sup>

**HOME ACCIDENTS AS A HEALTH PROBLEM.** The case for home accidents as a community health problem is readily made. Of all deaths from accidents among the civilian population of the United States in 1947, 35% were due to injuries sustained in the home, this being the largest among the four principal classes just defined. Of non-fatal accidental injuries, essentially a half were of that origin, 5,200,000 of a total of 10,520,000. Some 140,000 persons were left with a permanent physical defect as the result of a home accident. Thus for every death 150 others were temporarily disabled, more

than for any other class of accident, and 4 suffered a permanent impairment that varied from minor disability to complete crippling, these and other data being estimates of the National Safety Council. The death rate for home accidents in 1946 was 24 per 100,000 population. If the 4 classes of accidents are considered independently, home accidents alone are the ninth cause of death in the United States.

Other considerations add weight to these basic statistical data. For one thing, it is gradually being appreciated that the number of fatal accidents among workers is almost twice as great off the job as on.<sup>39a</sup> Of fatal accidents away from work one-fourth happen at home.

A second feature has to do with the major death rates for accidents of all forms among children less than 1 year of age and for adults past 65 years. Home accidents are the determining factor, for in 1947 no less than 62% of the accidental deaths in the older group were home casualties, while for children aged 0 to 4 years the proportion was 72%.

The data collected by Brown and his associates in Kansas and Nassau County, New York<sup>30c</sup> suggest another important relationship. Excluding infants under one year, where deaths of the sexes were essentially equal, the number of boys dying of home accidents at ages less than 15 years was twice that for girls, with reason to believe that the hours of risk in the home were much the same, and certainly no greater for boys. Males continued to have more fatal home accidents during the productive years, ages 15 to 64, although the numbers were more nearly equal. This occurred despite evident differences between males and females in the number of home hours at risk. A practical significance is brought out when this behavior is translated into working years lost, an excess not compensated by the

greater frequency of such fatal accidents among women at ages past 65 years.

**TREND OF HOME ACCIDENTS.** The trend of home accidents over the years is necessarily judged on the basis of deaths, because existing data are of that nature. In the early years of the century annual rates for accidents as a whole (Fig. 1) showed little evidence of a trend, but since 1930 the movement has been downward. At best no great improvement has been demonstrated. By excluding the currently

been shown by accidents in general, by those occurring in industry, nor even with the currently existing rates for motor accidents.

**A PUBLIC HEALTH APPROACH.** The need for a more energetic and reasoned advance on the health problem inherent in home accidents is believed clearly demonstrated.<sup>5</sup> This has been interpreted as an obligation of the medical profession, through organized public health agencies and the private practice of preventive medicine. The reason for that opinion rests in the

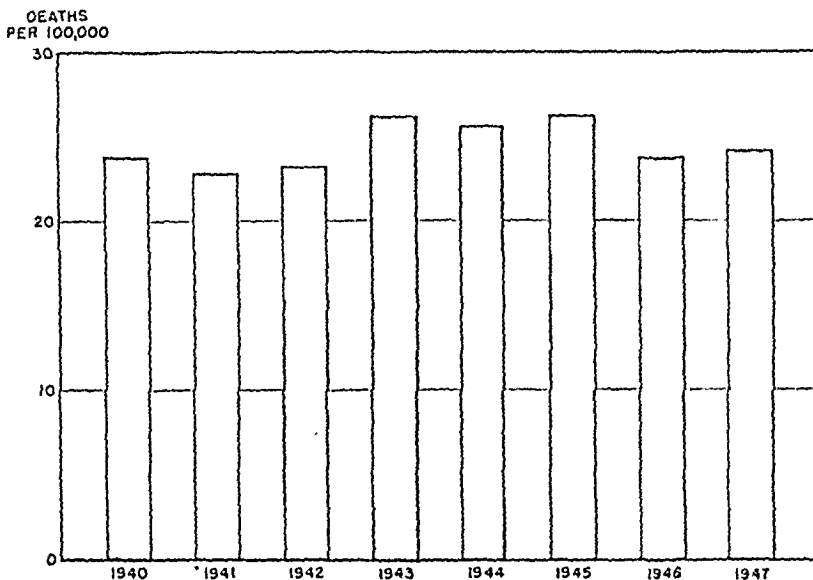


FIG. 2.—Home accidents, deaths per 100,000 population, United States, 1940-1947.<sup>30c</sup>

introduced factor of motor vehicle accidents, the record is better as shown by the dotted line in Fig. 1, but the gains have been in other fields than home accidents. For 1930 to 1947 the death rates for home accidents in the United States are remarkably uniform, usually about 24 deaths per 100,000 population per year, with a minimum for that period of 23 and a maximum uncommonly beyond 25, the highest rate being that of 29 in 1936. The experience of the present decade, as illustrated in Fig. 2, carries the single satisfaction that no ground has been lost. Home accidents have not kept pace with such improvement as has

current existence in most health departments of an organization, of facilities, and an experience in visiting the homes of people that is not possessed by other social or administrative agencies. Such a direct approach to the home is believed essential in determining first what the problem is and then in developing a preventive program primarily founded on health education. That again is a specialized field of organized public health.

If home accidents are a primary responsibility of community medicine, then it is reasonable to apply the technics<sup>35b</sup> upon which all community health practice is based, whether the



problem is of the communicable diseases, of cancer, diabetes, nutrition or other. In essence, this includes an initial epidemiologic analysis followed by a focal attack on the places and toward the situations where the condition has been demonstrated to be most pronounced. This is accomplished through specific educational procedures and the demonstration of preventive measures by public health nurses or other health visitors in the homes of people. The determination of commonly existing patterns of epidemiologic behavior is the first requisite. In presenting this method of medicine as an approach to the accidents that occur in homes, the suggestion is left that the same procedures may be applied to advantage in other fields of accident prevention not so clearly within the responsibility of the doctor.

The objectives of an epidemiologic analysis of home accidents are simple; first to find out when and where these events take place; secondly, how they occur, which is to say the mechanism involved; and finally, to learn who gets hurt. These matters are vitally practical. Preventive measures are costly. They are time consuming, and interest flags if return is not evident. If universally applied in blanket fashion, they lead to diffuse effort and minimal accomplishment. When deaths from tuberculosis in Detroit were judged some years ago to be beyond reasonable limits, the attack on the disease was not through a city wide campaign, but through search for those fractions of the population contributing in unusual degree to the total tuberculosis of the city. They were found in the population of 3 wards, where intensive control produced a significant improvement in the rates for the city as a whole. The reason for an interest in the patterns of home accidents, or any other community health problem, is to direct available preventive measures intelligently and specifically.

The study of patterns of behavior leads straight to the question of cause, which is more complex than the tangible object so commonly interpreted as the responsible factor in disease or injury, a microorganism in communicable disease or the loose board in a home accident. Rather it is a combination of forces from at least 3 sources, neither one nor the other regularly exerting the principal effect. These are the direct etiologic agent, the character of the host who develops the morbid process, and thirdly, the environment in which both exist, as it influences the interaction of the one with the other.

An organized effort to analyze home accidents as a community health problem comprehensively and on a national scale, has yet to be made. The necessity for repeated reference to estimates will have demonstrated the general lack of factual data. What facts exist have too often been brought together indiscriminately, with no direct objective of answering specific questions. The epidemiologic method of field study is a useful procedure in acquiring the necessary added information. An ecologic interpretation,<sup>22</sup> in terms of agent, host and environment suggests a framework within which to arrange available facts and more important to point to unexplored parts of the problem. A constructive program for prevention depends upon a broad definition of cause. Accidents are believed to be no different from any other mass health problem and hence to conform to general laws of biologic behavior. Similar situations consequently arise from dissimilar causes, they vary in time and in place, and each community needs the specific information derived from a study of local conditions upon which to build a logical and specific program of prevention.

**TYPES OF HOME ACCIDENTS.** Whether judged by the approximations of the National Safety Council<sup>23c</sup> or by the

data of Brown<sup>30d</sup> and others, the most common type of fatal home accident is death from falls, since they regularly account for somewhat more than half of all fatalities. Falls on the same level outnumbered falls from one level to another in the proportion of 3 to 2, and together were responsible in 1947 for more than 3 times as many deaths as the next most frequent type of fatal home accident, which was burns, scalds, and explosions. Death from mechanical suffocation surprisingly ranks third among causes of fatal accidents in the home, despite its limitation,

34,500 accidental deaths in the home during 1947.

**AGENTS CAUSING ACCIDENTS.** The accepted classification of home accidents by type gives all too little information about cause, for the first 3 categories are not descriptive of the things that cause accidents but of the mechanisms by which they took place. Even as mechanisms they lack detail of the activity<sup>30b</sup> in which the person was engaged. A burn may result from conflagration, explosion or scald, from hot liquids or hot solids; the recognition of

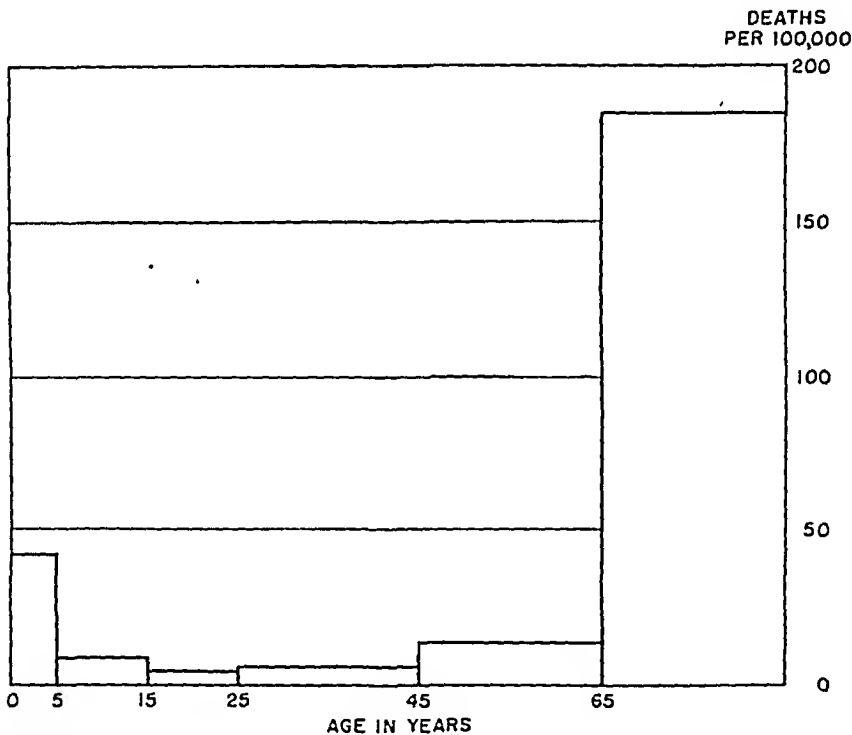


FIG. 3.—Home accidents, deaths per 100,000 population, United States, 1945.<sup>30c</sup>

in an estimated extent of 90%, to infants aged less than one year. More detailed studies<sup>1</sup> have shown a number of such deaths to be properly ascribed to other causes, such as infections, but the recorded total of 1,700 fatalities in 1947 marks this as perhaps the most striking among influences exerted by the age of the patient. Poisons except by gas, poisonous gas, and firearms follow in the order named, with these 6 forms responsible for some 85% of the

which of these was the cause has been shown by Schlesinger *et al.*<sup>35</sup> to be a practical consideration in understanding the home accidents of children. Mechanical suffocation may follow from bedclothes or beans; with falls all manner of agents may be considered such as wet or waxed floors, unanchored rugs, loose objects, ladders and stairs. More important is the recognition of faulty design, improper construction or poor repair of objects

about the home as the direct cause of accidents.

Poisons except gas, poisonous gas, and firearms are satisfactory designation of the agent and are susceptible to subdivision and specification. The study of the agent needs still further elaboration, for the things that cause accidents in rural homes are conceivably different from those acting in urban residences, and those concerned with children do not hold for aged persons. So far as known, only the Kansas State Health Department,<sup>26</sup> the Metropolitan Life Insurance Company<sup>6b</sup> and a few others<sup>30a</sup> are collecting data to answer these questions.

ties through the aging process and from disease, and consequently an increased liability to accidental injury. Aside from the deviations in anatomic and physiologic state, inherent differences exist among people, to the extent that some are recognized as unusually susceptible to accidents, a state termed accident proneness. The host patterns of persons who suffer from accidents are thus seen to be of the same general order as those long recognized for many disease processes.

*Age.* Like so many diseases where the host factor is an important consideration, deaths from home accidents are more frequent at the extremes of

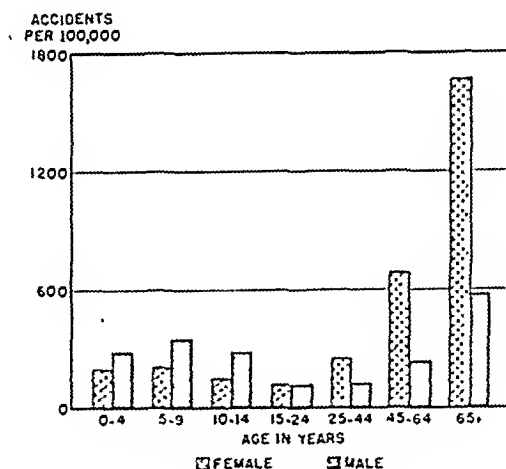


FIG. 1.—Home accidents from falls, per 100,000 population, by age and sex, National Health Survey, 1935-1936.<sup>12</sup>

**HOST FACTOR.** The common tendency is to look upon the person who suffers an accidental injury as the poor victim of circumstance, and yet the explanation of home accidents is believed more frequently to be found in what are called host factors, within people themselves, than in either the environment or the agents directly concerned. Age alone introduces evident difficulties in the ability of persons to compete with their environment. Infants and young children lack the necessary physical ability and experience. Older persons acquire physical and mental incapaci-

ties. The relationship is best defined where separate rates are computed for infants less than 1 year<sup>12b</sup> and for older children aged 1 to 4 years. Death rates for infants are commonly 3 and 4 times greater than for older pre-school children.<sup>12a</sup> For 1945 in the United States (Fig. 3) the home accident rate for all children under 5 years was 42.2. No other age group has the high rate of fatal accidents of persons aged 65 years or more, which for the same year was 155.0 per 100,000.

Reliable data on morbidity of home accidents are almost wholly limited to

facts derived from the National Health Survey<sup>11,12</sup> of 1935-1936. The distributional pattern for total cases by age is similar to that for death from accidents for the country as a whole. Individual types of accidents show pronounced differences. Accidental injury as the result of falls was a relatively minor consideration among children under 5 years, in relation to the total accidents they experienced (Fig. 4). It became an increasingly greater factor with advancing age, and for elderly people was far and away the predominating type of injury. Accidents resulting from cutting and piercing instruments led to an entirely different pattern (Fig. 5), in that children and young adults were principally affected and older persons in appreciably lesser degree.

accidental injury for the 15 to 24 year group, and rank importantly for the immediately preceding and following divisions. Falls were not represented in the youngest age but assumed increasing importance with advancing age, to become the leading cause of accidental death from home injuries at 45 years and thereafter. These varying distributions give added emphasis to the need for a comprehensive examination of causative factors to include host and environmental influences as well as agent.

**Sex.** For all groups through 24 years, home accidents are strongly a function of males rather than females, but thereafter females predominate and for elderly people in well marked degree, better than 2 to 1. The distributions

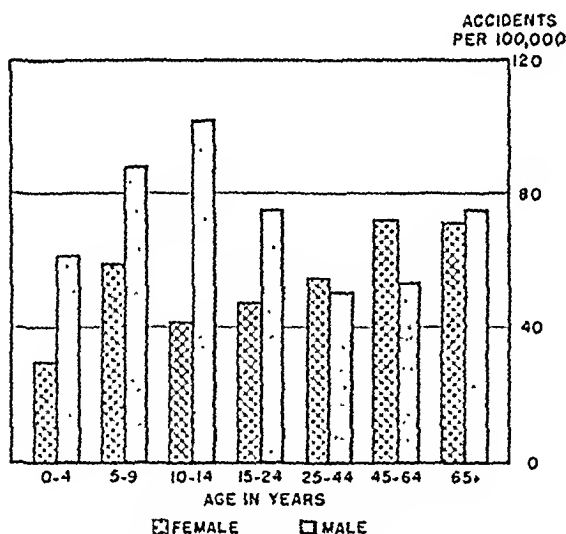


FIG. 5.—Home accidents from cutting and piercing instruments, per 100,000 population, by age and sex, National Health Survey, 1935-1936.<sup>12</sup>

These illustrations suggest the value of examining the types of fatal home accident that predominate at various ages. For 1945 burns were the principal feature at ages 0 to 14 years, and for all other age groups were among the four principal types. Mechanical suffocation and foreign bodies ranked second and third in the youngest age group, 0 to 4 years, but did not appear subsequently among commoner experiences. Firearms were the first cause of

that characterize falls (Fig. 4) are fairly typical of the general situation, but individual types of home accidents (Fig. 5) while continuing to demonstrate the principle of a dominance of males are nevertheless subject to quantitative differences.

**Race.** The national experience in the United States shows somewhat greater accident rates for colored than for white populations,<sup>13</sup> but less than for many mass diseases. They undoubtedly

reflect differences in economic position, geographic distribution and occupational distributions of the races. Selected types of home accidents serve particularly well in demonstrating these differences; for example mechanical suffocation, where the rates for colored infants under one year are twice those for white children of that age.

*Acquired Susceptibility.* The greater probability of accidents for persons under the influence of alcohol has been studied almost exclusively in relation to motor vehicle accidents. The observations of Joss<sup>25</sup> in Minneapolis show this factor to act also in other types of traumatic injury, but so far as known, its significance in home accidents has not been investigated. Industry has given attention to other forms of acquired susceptibility, such as those resulting from fatigue, impairment of vision, and deficiencies of hearing, but again the situation is unexplored in home accidents.

*Inherent Susceptibility.* Collected experience, principally in relation to motor accidents<sup>20,31</sup> has demonstrated that certain individuals have repeated accidents, and that multiple accidents by a relatively limited group contribute materially to the whole. This condition, represented by a tendency toward accidents, has been termed accident proneness.<sup>21,25</sup> Neither reaction time, intelligence, physique, nor skill<sup>27</sup> appears to have any part in its origin as an inherent constitutional attribute. It is suggestively distinct from the frequency of accidents associated with an unfamiliar environment, as evidenced by workers undertaking new tasks,<sup>11</sup> or youths learning to drive automobiles, since an improved or extended experience fails to remedy the situation. Such individuals continue to have accidents in whatever occupation they engage and presumably under the varying situations in which they find themselves. The existence of the condition is only to be recognized by the

record of past performance, although variously studied by psychiatric methods. Its significance in home accidents has not been investigated.

*ENVIRONMENT.* The primary classification of accidents on the basis of the places they occur is of itself indication of the importance of environment as a factor in causation. The concept of environment as composed of three major elements,<sup>22</sup> the physical, the biological, and the socio-economic environment, will be followed in interpreting accidents as a result of the competition between man and his environment. The physical environment has to do with matters of climate and weather, of season and topographical affairs, with soil and other physical features of the world where man lives. The biologic component can be taken to include the universe of living things that surrounds man, all else than man himself; while the socio-economic part of environment is that which comes into play through association of man with his fellow man. Environment so considered exerts an influence on disease and injury sometimes through direct action on host or on agent and sometimes on the mechanisms which bring host and agent together or determine their interaction. The results of environmental influences are to be measured by the character of the process that results, by the extent and nature of the frequencies that follow and often by both.

*Geographic Distributions.* Differences in frequency of occurrence according to geographic regions are characteristic of many mass diseases. Injuries typified by accident show a similar behavior. For all accidents, the western states of America have consistently higher rates than the areas to the east of the Mississippi River, with the mountain states exceeding any other region (Fig. 6). The vacation states of Florida, Vermont and New Hampshire

rank well above the average for the country. Connecticut establishes the best record for 1947 with 50 deaths per 100,000 population, while Nevada with 137.6 is high. Of the 9 standard groupings by which states are commonly distributed for statistical purposes, the middle Atlantic group including New York, New Jersey and Pennsylvania, and the New England states have the best records.

The less comprehensive information about home accidents indicates similar differences in distribution from one part of the country to another. Rates

The gross differentiation by states scarcely permits the individual community to judge its particular problem of home accidents. Much depends on the concentration and character of the population, as becomes evident when the frequency of home accidents is considered in relation to place of residence, as urban, farm<sup>13</sup> and rural non-farm,<sup>33</sup> for home accidents are clearly a greater problem of urban communities than rural non-farm areas (Fig. 7). The reasons are not well defined but the differences are sufficiently great to suggest material variations from com-

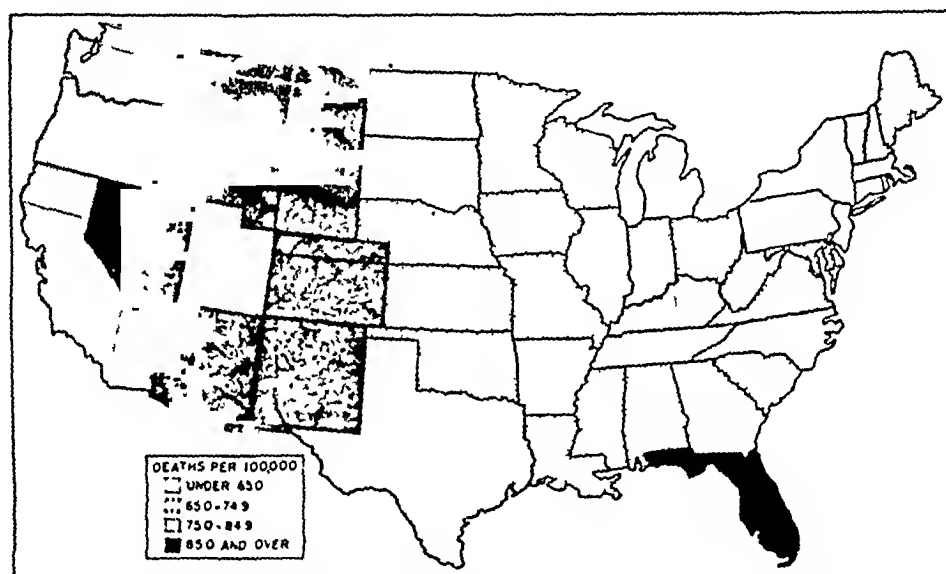


FIG. 6.—Accidental deaths, per 100,000 population, United States, 1917.<sup>30c</sup>

varied in 1947 from 34.5 in Missouri to those of Utah with 16.8 home fatalities per 100,000 population. Little correlation exists between total accident deaths and those for home accidents. The total rate for Utah was high, 82.9, and yet of 27 states separately reporting home accidents it had the best rate. Missouri with the highest rate for home deaths had a wholly ordinary total rate of 74.5, although 46% of reported accidents were in the home. New York had almost an identical proportion of home accidents (45.5%) but the total rate was among the best in the United States (59.7 per 100,000).

munity to community. This has been recognized to the extent that some few cities have determined the frequency of fatal home accidents by subdivision, such as wards or census tracts, and states like Tennessee<sup>10</sup> and Kansas<sup>20</sup> have effected divisions by counties. The result emphasizes the need for individualized information if communities are to apply proper emphasis in control measures.

Largely because of the interest of a few investigators, much is known of the inner structure of the home as an environmental factor in home accidents. The data from Kansas and Long Island<sup>30d</sup> show bedrooms to be the

most common location of fatal accidents, because most deaths of infants and persons past 75 years occur there, and for both the total numbers are great. The next most favored site was the yard about the home, and close thereafter the kitchen. Stairs are a natural hazard, with the remaining parts of the home measurably less important. The studies of the Metropolitan Life Insurance Company<sup>39a</sup> led to the conclusion that the kitchen is the most dangerous room in the house. An estimate of 6,000 annual deaths is given. The injuries that occur are likely to be severe and a wide variety of exposures is evident, for this is the

tion, specific kinds of home accidents as a whole do experience seasonal fluctuation, for instance the deaths of infants from mechanical suffocation, and from falls at all ages, during the winter months. Generally, the information about distributions in time is none too extensive, especially for non-fatal accidents. Knowledge of home accidents would profit by the methods used in the study of motor vehicle accidents to determine such time factors as the influence of weekends, of holidays, of periods of bad weather, and of the shifting hours of daylight and darkness.

*Socio-Economic Environment.* Whatever the kind or nature of mass disease

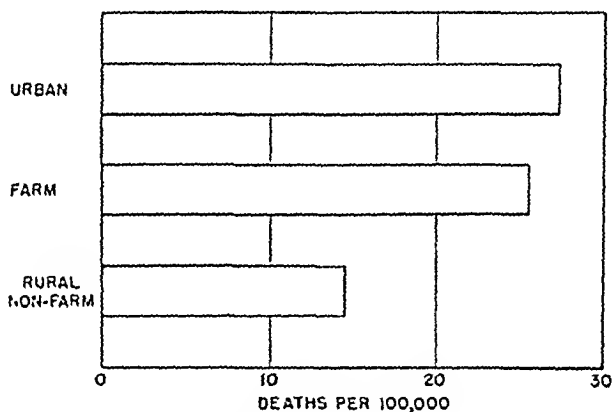


FIG. 7.—Home accidents, deaths per 100,000 population, by place of occurrence, United States, 1917.<sup>30c</sup>

factory of the home, the center of domestic activities. The demonstration of the specific kinds of hazard that pertain to various features of home life have permitted direct educational<sup>39c</sup> measures against demonstrated causes and the places they are active.

*Distributions in Time.* Home accidents when judged by existing frequencies from year to year (Fig. 2) are a steadily recurring phenomenon, corresponding to the endemic behavior of disease. The variations from month to month are likewise minimal as illustrated by the experience of Wisconsin for 1916 (Fig. 5). Although accidents as a whole show no seasonal predilec-

tion, whether it be infectious, metabolic, or traumatic the part exerted by the socio-economic environment is probably the most neglected and underdeveloped of any epidemiologic influence, with accidents no different from any other. Only scattered information can be put together, that arising from the National Health Survey of 1935 being the most constructive.<sup>9,10</sup> The quality of housing, as judged by the amount of income or rental paid, has been repeatedly demonstrated to have an influence on the frequency of both communicable and non-communicable disease. It is not surprising that the same causative influence is shown

in the frequency of accidents; the lower the standard of housing the greater was the frequency of home accidents. Indeed, many of the physical factors of environment already considered, and those of the host will be seen scarcely to act independently but are representative of a solid admixture with this important component of socio-economic environment.

**EPIDEMIOLOGIC METHOD APPLIED.** Each of the 3 broad factors in causation has been considered individually to the end of demonstrating principle. But the illustrations themselves and more particularly the concept of epi-

A principal difficulty is in unearthing the index case, for case finding through the system of reporting so useful in the study of communicable disease and some few other conditions, is not available for accidents. Officially filed death certificates relating to accidental deaths are one source of information. Patients admitted to the accident services of hospitals are another. The kind of information basically essential to a comprehensive preventive program is that which relates to the bulk of lesser events, the accidents that result in temporary and often minor disability. This is to be obtained most surely

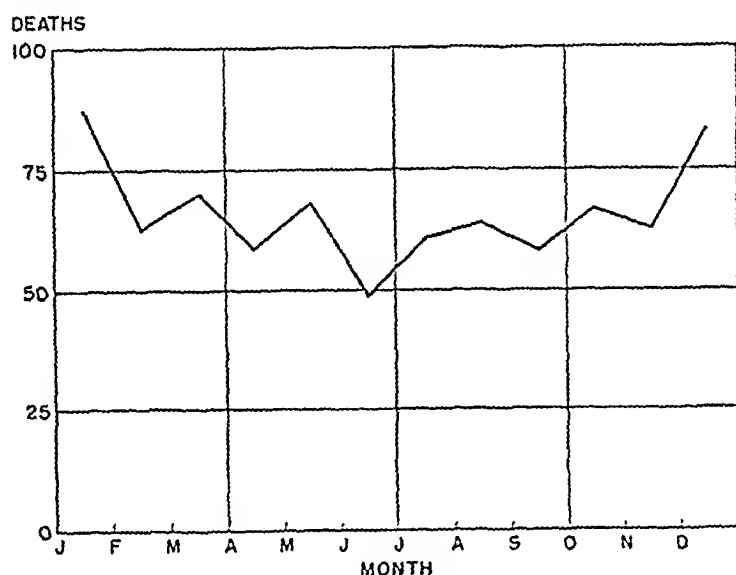


FIG. 8.—Deaths from home accidents, by month, Wisconsin, average 1946 and 1947 (Source: Wisconsin State Board of Health).

demiology as medical ecology, show this to be an oversimplification. All 3 factors are intimately interwoven, each influenced by the other. The important consideration is that accidents as a community health problem give evidence of conforming to basic biologic laws, that they are the result of the total forces within a universe, of an ecologic entity, of the competition between man and his environment. This calls for epidemiologic analysis as the practical approach to improved understanding and to a specifically directed prevention.

through organized survey and special studies in selected areas. If facilities are not available for such comprehensive investigations a fourth source of index cases is to be had by incorporating the investigation of accidents into the ordinary activities of health departments, where public health nurses and others include a consideration of accidents along with other activities which take them to the homes of people. The choice of method depends largely on the facilities available and the local interest that exists. Something more is needed for an adequate preventive pro-



gram than a knowledge of fatal accidents or of persons seriously injured. The organized survey is the most productive but much can be accomplished by the alternative procedure last mentioned.

Whatever the decision as to the scope of activities deemed practicable, the procedure is the same, an individual case study of the patient, the family group, and the immediate surroundings in which they live. The technic is fundamentally that so well developed for communicable and other diseases. The nature of the accident is determined, the result evaluated in terms of death or recovery, and of temporary disability or permanent defect. The causes are sought through direct investigation of the site of the accident, of the associated circumstances and of the person who was injured. Investigation, forms of the type used in Kansas provide a simple means for acquiring and recording the necessary data.

The same considerations of local need and available resources govern the comprehensiveness of data to be collected and analyses to be made. It is within the resources of almost any health department to obtain the simple information about age, date, type of accident, ages involved, and the nature of the injury. Simple correlations may be made of type of accident with age of the patient, with the activity in which he was engaged, of the location within the house, and of the house within the jurisdiction. It is hoped that some few investigators will be able to undertake more comprehensive studies of causation, with as much attention placed on the part played by the host and such fundamental features of the environment as are concerned with socio-economic conditions. It is desirable that these correspond to representative regions within the United States and to varying concentrations of populations in sufficient number to provide the information so clearly needed

for a better definition of the laws of accident production.

**THE PROGRAM OF PREVENTION.** The emphasis which has been given to the epidemiologic approach to accidents has the wholly utilitarian purpose of permitting a more reasonable program of preventive action than is now possible from existing information. Causation needs to be explained, not in the limited sense of the direct agent, but through consideration of the multiple factors inherent in the host, the agent, and the environment. The pattern of study that has been outlined is to that end.

The principal instruments of a preventive program<sup>35a</sup> are rather clearly public health education,<sup>28</sup> the demonstration of existing accident hazards in the home, and direct instruction in the means by which they can be corrected.<sup>6a</sup>

The emphasis thus far has been on what may be done by governmental agencies and official health departments. As with all health activities which involve personal services, the greatest potential promise of accomplishment in accident prevention is through the private practitioner of medicine, in his contact with the families of his community.

A final word about objectives may be useful. Public health activities are directed to the prevention of disease and injury in the community. Circumstances commonly require a similar compromise as in clinical medicine, namely the need to be satisfied with something less than the perfect result; to control and limit disease that cannot be prevented, and when neither is possible, to decrease the costs in terms of permanent defect. All are a positive contribution, although in progressively lesser degree. No assumption is made that all accidents can be prevented, but much can be accomplished in decreasing the health losses from that cause.

No useful additions can be made to the suggestions for home safety activities by local health departments that have been advanced by the Subcommittee on Accident Prevention<sup>3b</sup> of the American Public Health Association. They stress the need for more informa-

tion, and advice is logically given in procedures that can now be applied with what information is at hand. Only through a better understanding than now exists of what to educate against, and what measures to demonstrate, can these procedures be put into full force.

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# PATHOLOGY AND BACTERIOLOGY

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## IMMUNIZATION WITH MIXED BACTERIAL ANTIGENS

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THE past war, as was the case with its predecessor, served as a strong stimulus to the widespread investigation of the use of combined antigens for prophylactic immunization. This was to be expected in that the practical advantages to be gained by such procedures in the mass immunization of populations or groups of the population are obvious and become a pressing need under wartime conditions. Studies initiated by World War I were carried on between the wars and this will doubtless prove to be the case once more, and on even a greater scale, since viral and rickettsial infections are now receiving their due attention in this respect. However, it is of value to attempt to measure and report the progress made after a period of activity in any field, and this would appear to be an appropriate time to do so in regard to work dealing with the use of mixed bacterial antigens.

The initiation and study of the use of combined bacterial antigens for prophylactic immunization was for many years retarded and hampered by widespread acceptance of the theory that such efforts would fail to produce a good response to each component inoculated, or that the response to each component would be much less satisfactory than that following their separate injection. This theory as to the

"competition of antigens" had its basis in the work of Michaelis<sup>21</sup> who in 1904 demonstrated that the injection of untreated blood serum resulted in only slight antibody production against albumin, but good precipitin for globulin. Immunization with the albumin fraction alone resulted in a large precipitin production. Support for this attitude was provided by Friedberger<sup>15</sup> the same year, using combined typhoid and cholera vaccine, for he claimed that this resulted in cholera antibody formation being 6 to 37 times lower than when cholera vaccine alone was employed. More recent evidence of the same nature has been provided by Zlatogoroff *et al.*<sup>41</sup> in 1929 and by Scheibel<sup>30</sup> in 1944. Their experiments were carried out in guinea pigs using diphtheria and tetanus toxoids and the conclusion was that immunization with 2 antigens would result in a lowered response to at least 1 of them. However, this effect was most noticeable with small doses and few injections and raises the possibility that the different response was essentially due to differences in threshold rather than competition between antigens. Scheibel also was of the opinion that his findings did not present a complete barrier to human use of such mixtures, in that even with some reduction in antibody formation, the amount produced for both

components was sufficient for effective protection.

These studies cannot be disregarded, but at the same time the great majority of reports do not demonstrate adverse results from the inoculation of combined bacterial antigens. In fact the reverse is the case, for more recently the most striking feature of such studies has been the discovery that the response to some or a number of components in a mixture will be actually enhanced by their employment as a constituent of a mixture rather than as a single entity for immunization.

There would appear to be some dispute as to which worker should receive credit for initiating the long series of studies dealing with the use of multiple antigens in prophylactic vaccination. On the evidence available, Castellani<sup>8</sup> would appear to have earned this distinction, for in a paper published in 1915 he cited publications by him in the preceding 15 years in this field. In 1901-02 he claimed to have demonstrated that rabbits inoculated with several species of bacteria developed agglutinins for each to as great an extent as control animals receiving only one species by inoculation. This result led him to introduce the use of a combined typhoid, paratyphoid A and B vaccine in Ceylon in 1905 and to the later addition of killed cholera vibrios to the mixture. By 1915 it was possible to report<sup>7,8</sup> that some 170,000 individuals had been immunized with this "tetravaccine" in Serbia. Castellani did not restrict his investigation to the vaccine components already described, but also investigated combinations of up to 6 constituents and stated that some 14 combinations of 2 or more antigens had been used in humans. In 1916 a similar study was reported by Weber,<sup>39</sup> who claimed that immunization with mixed cholera-typhoid vaccine produced as high agglutinin titers for both antigens as were obtained in

controls receiving separate inoculations of each antigen.

Although these pieces of work must receive historical precedence, the most noteworthy attempt to demolish the theory of antigenic competition came from a series of reports by Ramon and Zoeller<sup>32 a-f</sup> in 1926 which were summarized by Ramon in 1939.<sup>33</sup> This work showed that the inoculation into animals of a non-specific adjuvant such as tapioca, calcium chloride or alum to an antigenic substance such as diphtheria toxoid resulted in the host giving a much improved response to the antigen as measured by specific antibody production. This observation was then applied to animals, and later to humans, in the inoculation of such unlike materials as diphtheria toxoid and typhoid vaccine. It was then established that satisfactory polyvalent immunization could be produced by the simultaneous inoculation of typhoid vaccine, diphtheria and tetanus toxoids. Similar studies were reported in 1935 by Ando and Nagata<sup>1</sup> who found that alum precipitated scarlet fever and diphtheria toxoids produced in rabbits as good a response in combination as alone; and in 1940 Schutze<sup>37</sup> who reported that in guinea pigs the antigenic potency of alum precipitated diphtheria toxoid and pertussis vaccine was not impaired by combination in a mixture for immunization. The possibility that mixing of antigens might have a deleterious effect upon the components of the mixture was shown to be without foundation, at least in regard to a mixture composed of the organisms responsible for typhoid and paratyphoid fevers A, B and C when combined with tetanus toxoid and stored for any reasonable period of time.<sup>17</sup>

These and similar studies have provided the experimental basis for the intensive investigation of the use of combined antigens for active immunization against bacterial diseases in which this approach has proved either

feasible or justifiable on the basis of need for such protection. Although many combinations of such bacterial antigens have been subjected to investigation, the major attention of the past two decades has been directed to certain specific diseases, namely: the typhoid and paratyphoid fevers, diphtheria, whooping cough and tetanus. At this time it is proposed to present evidence that has been produced in regard to the status of combined immunization in each of these infections of major interest to medicine on this continent and to discuss some of the general problems of combined immunization that have arisen as an unforeseen consequence of studies more narrowly directed.

The customary age distribution of cases in the diseases just mentioned has tended to divide immunization studies rather sharply into 2 categories. Those concerned with prophylaxis against the typhoid and paratyphoid fevers have dealt with adult groups; those dealing with diphtheria and whooping cough have been concerned with the infant and child elements of the population. The original conception of tetanus as an adult hazard resulted in its being of concern to the first group, but a more recent appreciation of the significance of this disease in childhood has had the effect of sharing of interest in this disease by all concerned with combined immunization.

The tremendous value and great effectiveness of typhoid vaccination was firmly established in World War I, although extensive British experience with typhoid vaccine had begun with the South African War. At that time the results were not convincing in regard to lessening of incidence of enteric infection in the recently immunized troops, but the case mortality rate was reduced from 16.6% to 8% in that group as compared to uninoculated controls. A very striking reduction of both incidence and mortality from

enteric fever was demonstrated in the period 1909-1913 when British troops serving in India were practically all inoculated with typhoid vaccine. Very complete records exist of British experience with typhoid and T.A.B. (typhoid, paratyphoid A, paratyphoid B) vaccine in the first World War.<sup>29</sup> At the beginning of the war in 1914 only some 30% of troops had received a single inoculation of typhoid vaccine, but this was gradually increased to over 90% by the end of the next year. Early in 1916 T.A.B. vaccine was introduced and its use in 2 doses of 0.5 cc. and 1.0 cc. at 10 and 14 day intervals replaced simple typhoid vaccine for the remainder of the conflict. During 1915, when protection against only typhoid fever was provided, the incidence of this disease in those immunized was less than one-tenth that occurring in the uninoculated and there was evidence of a considerable degree of protection against paratyphoid fevers A and B as well, particularly in regard to mortality from those diseases. In the final year of the war, when fully 95% of some 2½ million men were fully protected with T.A.B. vaccine, the incidence of enteric disease was reduced to only 376 cases.<sup>38</sup> French and American experience provided confirmation for these striking results.

The satisfactory results thus demonstrated were more than duplicated in World War II. In a recent report<sup>28</sup> it has been stated that fewer than 50 cases, with only 2 fatalities, occurred in an army of over 3 millions.

The widespread adoption of typhoid vaccine, later followed by the incorporation of the organisms responsible for the paratyphoid fevers, was a major development. Although it is true that such vaccines are mixed vaccines in every sense of the word, the fact that the elements composing them were bacterial cells of somewhat similar morphological and cultural characteristics and the causative agents of

clinically similar diseases tended to blunt the impact of this important innovation; though it probably prepared the ground for the acceptance of large-scale use of more unusual mixtures for prophylaxis of other diseases recognized as being of major significance in military medicine. This further step could only be taken if it were possible to demonstrate that the effectiveness of vaccination against the enteric infections was not impaired by the new constituent of the mixture.

The importance of diphtheria as an endemic disease in France led to the introduction of compulsory immunization for diphtheria among French troops in 1931 and studies were soon undertaken to demonstrate the possibility of combined immunization. The results were satisfactory and in one study<sup>12a</sup> it was reported that the attack rate of diphtheria per thousand men was reduced from 10.7 in the unprotected to 0.84 in those immunized with the combined material. As a consequence of these and other findings<sup>12b,34</sup> it was decided that combined immunization should be the recommended procedure for primary immunization of recruits.

As was to be expected, the importance of tetanus greatly outweighed that of diphtheria in the eyes of those concerned with active immunization of adults, and this was particularly the case in regard to members of the armed forces. As a consequence, the vast majority of studies dealing with the combination of typhoid-paratyphoid vaccine and other antigens have been concerned with a mixture incorporating tetanus toxoid as a major constituent. The value of tetanus antitoxin as a prophylactic agent was shown in World War I when its introduction resulted in the incidence of tetanus falling from 8 to 1 per thousand wounded.<sup>6</sup> However the demonstration that active immunity could be established by the use of tetanus toxoid en-

couraged studies of this approach to the problem between the wars, since there were great disadvantages to any plan of prophylaxis which placed complete reliance upon the administration of passive immunization to wounded in the field. Active immunization would also tend to eliminate the problem created by hypersensitivity to horse serum. At the beginning of World War II sufficient work had been reported<sup>9, 10b, 22, 34</sup> to justify the conclusion that tetanus toxoid could be combined with other antigens for effective immunization against all components of the mixtures. Reports have since appeared as to the great effectiveness of active immunization against tetanus under war conditions. Boyd states<sup>6</sup> that in the British Expeditionary Force of 1939-40 in Europe there were 7 cases of tetanus in the non-immunized 10% and no cases in the immunized 90%. A quotation from a paper by Montgomery<sup>23</sup> is even more striking: "Perhaps the most dramatic advance in preventive medicine was encountered in the protection given by tetanus toxoid. It was given to all Canadian and American soldiers at the same time as the T.A.B. vaccine. To my knowledge, no authentic case of tetanus developed in the Canadian Army overseas, and Colonel Wm. Middleton, Chief Consultant in Medicine, European Theatre of Operations, U. S. Army, is authority for the statement that only 1 instance of tetanus occurred in the American Army. The Nazis afforded the perfect control. Only the Luftwaffe and certain paratroop elements received tetanus toxoid. Of the unprotected German prisoners-of-war, hundreds developed tetanus and scores died in Allied hospitals." To sum up, one may say that the incidence of tetanus was reduced to negligible proportions by active immunization, though it is still a matter of some dispute as to whether the wounded man should also receive tetanus antitoxin or complete reliance be placed upon a

reinforcing inoculation of toxoid at the time wounding occurs.

Despite the significance attached to tetanus as a problem of military medicine, there has been increasing attention paid to its occurrence among civilian groups. In 1938 Cooke pointed out<sup>10</sup> that in 1930 the mortality rate from tetanus in the United States was 1.1 per 100,000 of population and that, although children constituted less than 30% of the population, more than half the tetanus deaths were in childhood. This statement was at variance with the conventional belief that tetanus was a hazard of ordinary life only when occupation, such as farming, created a special need for protection. The fact that reliance could not be placed upon routine use of tetanus antitoxin at the time of injury was stressed by Pratt<sup>31</sup> in an investigation of 56 cases of tetanus. He found that in 60% of these patients the original injury was of such a nature that prevention would not be achieved by the application of conventional measures in that the injury was not appreciated or was of such a nature as not to demand prophylactic procedures. However, acceptance by the medical profession of these views would by itself achieve little, since it is unlikely that the general population would accept routine active immunization procedures specifically directed against tetanus in view of the relative rarity of this disease in civilian life. At the same time, the general acceptance of prophylactic immunization against certain other diseases affords an opportunity for production of the desired protection against tetanus provided tetanus toxoid can be administered simultaneously and without deleterious effect upon the other antigenic components of the mixture.

The need for exact information on this point has stimulated a number of studies dealing with the effectiveness of tetanus toxoid when combined with diphtheria toxoid and pertussis vaccine,

the antigens routinely used in the prophylactic immunization of infants and children. Results of studies reported by Peshkin;<sup>30a,b</sup> Bigler and Werner;<sup>3</sup> Deamer *et al.*;<sup>11</sup> Lapin;<sup>21a,b</sup> and by Miller and his associates<sup>26,27</sup> have all demonstrated a satisfactory response to tetanus toxoid and no appreciable interference with the other components of the various mixtures employed. The studies of Peshkin<sup>30a,b</sup> are of particular interest in that they deal with the response to such active immunization by a group of 186 allergic children who might be expected to present a serious problem were the need for passive immunization to occur in the future. Some 94% responded satisfactorily to 2 inoculations of the combined alum precipitated diphtheria and tetanus toxoids used in these studies and of the remaining 6%, all but 1 child gave a satisfactory response to a third inoculation. Even after 2 years, nearly half of these children had an adequate level of tetanus antitoxin and there is no question but that a reinforcing inoculation would result in a good response from this group on the basis of results reported by Bigler and Werner<sup>3</sup> and Miller and Ryan,<sup>27</sup> when the response of the immunized child to such a stimulus was measured.

The general acceptance of the value of diphtheria toxoid demanded thorough investigation before the addition of other antigens to this material could be advocated. It has long been held that a combined immunization against diphtheria and whooping cough would be most desirable, if it was practicable, and the more recent interest in active immunization against tetanus has reinforced the need for investigation of this problem. The early work of French investigators,<sup>12a,b; 32a-f</sup> using a combination of diphtheria toxoid and typhoid vaccine was a hopeful augury for this approach to the needs for active immunization in the infant and child population. In 1934 Ingels<sup>13</sup> confirmed



French experience by showing that 90% of a group of 3,000 elementary school children had been rendered Schick negative by a course of combined diphtheria-typhoid immunization. Bordet in 1936<sup>5</sup> was the first to report the use of a mixture of diphtheria toxoid and pertussis vaccine; but he provided no data on immunity tests for either disease, nor did he report clinical evidence of protection. Since 1942 a number of studies concerning the combination of diphtheria toxoid with other bacterial antigens have appeared and certain of these can be referred to as illustrative of the results obtained.

Kendrick<sup>20a,b</sup> has reported extensive field studies involving more than 6,000 children in which pertussis vaccine has been used alone and in combination with diphtheria toxoid. Her results indicated a satisfactory response for both antigens, whether administered singly or combined, based upon diphtheria antitoxin titers and, in the case of pertussis vaccine, upon both laboratory determinations and actual incidence of whooping cough in immunized and control groups of children. These results have been supported by Lapin<sup>21a</sup> who administered a combination of fluid diphtheria toxoid, alum precipitated tetanus toxoid, pertussis vaccine and pertussis toxin to 78 infants of 6 to 9 months of age. Deamer *et al.*<sup>11</sup> immunized over 600 infants with combined diphtheria and alum precipitated tetanus toxoids and found that, under the conditions established, 96% were rendered Schick negative. Sauer *et al.*<sup>35</sup> carried out studies using mixtures of both plain and alum precipitated diphtheria toxoid and pertussis vaccine. The response, as judged by negative Schick tests and strongly positive *H. pertussis* complement fixation tests, was very satisfactory and gave strong support to the use of the combined product for immunization. The response to the alum precipitated mixtures was some-

what better, particularly as regards pertussis antibodies, but the greater severity of reactions would tend to make the plain mixture the product of choice. Miller and his associates<sup>26,27</sup> have reported the use of a combination of aluminum hydroxide adsorbed diphtheria and tetanus toxoids containing pertussis vaccine in a group of 126 children. These have shown an extremely good response to the toxoid components of the mixture and a fairly satisfactory response to the pertussis vaccine, which was improved in a second group of 103 children by increasing the dosage of that component. In 1946 Foley<sup>14</sup> reported a study covering a 3 year period in which more than 38,000 children of 6 months to 10 years of age were inoculated with combined diphtheria toxoid and pertussis vaccine. The protected group in the population showed a tremendous reduction in the morbidity from both diphtheria and whooping cough as compared with the non-protected population and there was no mortality from either disease in those immunized. Some 3,000 of those immunized also received a reinforcing inoculation and no case of either disease was known to have occurred in this group. The results of this extensive experience, under field conditions where both diphtheria and whooping cough were prevalent, allowed the conclusion to be made that the combined immunization does not lower the protection afforded by diphtheria toxoid and that it gives appreciable protection against whooping cough. Recent studies by Bell<sup>2a,b</sup> in which he used an alum precipitated mixture of diphtheria toxoid and pertussis vaccine have confirmed this impression of immunizing effectiveness, although here again the protection established against whooping cough is not as effective as that produced against diphtheria.

A matter of some importance in regard to combined immunization against diphtheria and whooping

cough has to do with the need for protection against the latter disease at the earliest possible opportunity. The importance of whooping cough as a cause of death in the first year of life makes it imperative to establish immunity at an earlier age than has been customary in the past for diphtheria toxoid in most public health programs. Some doubt has been expressed as to the effectiveness of active immunization when carried out before an infant is at least 6 months of age. In this respect, the report in 1948 of Fleming *et al.*<sup>13</sup> showing a satisfactory response to immunization in a group of infants averaging 4 months of age would appear to be of significance as indicating the possibility of producing active immunity against whooping cough at a time when it is of greatest value; and yet not interfering with the more widely accepted value of active immunization against diphtheria by combined inoculation at this early age.

At this point, consideration has been given to those procedures carried out to produce effective active immunization against two or more bacterial infections by combination of immunizing materials. In the course of these studies a number of observations of a more general nature have been made which demand attention in that their importance is such that they will very markedly affect any attempt to introduce combined immunization as an acceptable, routine procedure for general use in the population.

One such matter, of concern to physicians and laity alike, is the effect of mixing of antigens upon the severity of reactions, either local or constitutional, which may be expected to occur in patients receiving such materials. In 1937 Jones and Moss<sup>19a</sup> demonstrated a satisfactory immune response in 41 adults who received 2 inoculations of combined alum precipitated diphtheria and tetanus toxoids; but they felt that the reaction to the combined material

was more severe than when the constituents were employed individually. Peshkin, in his study<sup>30b</sup> of 65 allergic children, stated that the incidence of local reactions was about 25% with repeated inoculations of combined alum precipitated diphtheria and tetanus toxoids, but that no allergic reactions such as urticaria or asthma were encountered. Sauer *et al.*<sup>35</sup> reported the occurrence of a "sterile abscess" in 2% of injections, using combined alum precipitated diphtheria toxoid and pertussis vaccine. They felt that this was reason for advocating the use of the plain mixture, even at some expense to the immune response. However, these reports of increased severity of reaction are definitely in the minority.

Sacquépée *et al.*<sup>34</sup> reported absence of marked reactions in seven thousand adults who received combined inoculation against typhoid and paratyphoid fevers, diphtheria and tetanus. MacLean and Holt<sup>22</sup> felt that injection of tetanus toxoid and T.A.B. vaccine produced no more severe reactions than would result from the use of the vaccine alone. Bigler and Werner<sup>3</sup> had the same opinion concerning the addition of tetanus toxoid to diphtheria toxoid. Chen<sup>9</sup> found that the inoculation of combined T.A.B. vaccine and fluid tetanus toxoid was less irritating, and a more efficient antigen, than alum precipitated tetanus toxoid in guinea pigs. Lapin,<sup>21b</sup> Deamer *et al.*<sup>11</sup> and Fleming *et al.*<sup>13</sup> all report the absence of severe reactions in infants and children receiving various combinations of antigens. This would appear to be sufficient evidence to justify the belief that mixing of antigens does not increase the incidence or severity of reactions to the products and, therefore, will be no barrier to their adoption for general use.

A question of greater interest has to do with the rapidity and duration of response to combined antigens as com-

pared with that produced by the individual components of such mixtures. That is, will the reduction of material inoculated of each constituent in a mixture, or the necessity of altering the spacing or number of inoculations usually found desirable, have an adverse effect upon the immunity level attained for each component of the mixture? The evidence available provides reassurance on this important matter.

MacLean and Holt<sup>22</sup> report that when tetanus toxoid is combined with T.A.B. vaccine and given in 2 inoculations spaced a month apart, the response to the T.A.B. vaccine was just as satisfactory as when T.A.B. vaccine is administered at the customary weekly interval. Bell has shown<sup>2a</sup> that failures to immunize children with alum precipitated diphtheria toxoid, given in 1 or 2 inoculations, were 3 times as great as in the case of children who received the same number of inoculations of a combination of alum precipitated diphtheria toxoid and pertussis vaccine. The same picture of greater effectiveness for the combined product could be related to the age at which the children were immunized; for children, who received 2 inoculations of the combined product before they were 6 months of age, had fewer failures to immunize against diphtheria than children who received diphtheria toxoid alone at any age up to 23 months. The large-scale field study of Foley<sup>14</sup> provides strong evidence that combined immunization against diphtheria and whooping cough does not lower the protection against diphtheria which could be effected by diphtheria toxoid alone, nor does it interfere with the response to subsequent reinforcing inoculations. Various studies<sup>25,27</sup> have shown satisfactory protection against whooping cough over a lengthy period of time following combined immunization and similar reports have appeared<sup>3,11,30a,b,34</sup> in regard to the level of

tetanus antitoxin established by this method.

The early opposition to the use of combined antigens, provided by the supporters of the theory of antigenic competition, was swept aside when it was demonstrated that concurrent immunization against 2 or more antigens could be readily achieved. However it has become possible to adopt a more positive approach to the use of combined antigens in the past 2 decades as a consequence of the introduction of the hypothesis of antigenic synergy. The experiments of Ramon and Zoeller<sup>32c</sup> with mixed vaccines provided the basis for this new approach, in that the results obtained with combinations of antigens were better than could be expected from the individual components of such mixtures. Support for this viewpoint was furnished in 1928 by Weinberg *et al.*<sup>40</sup> when they immunized guinea pigs with mixtures of 2 species of clostridia and found that the antibody titers were only slightly lower than those observed in controls which had received considerably larger doses of single antigens. It would be reasonable to assume that there is a physical limitation placed upon such synergistic action and in 1941 Bjorneboe<sup>4</sup> produced evidence that this was the case. After demonstrating that rabbits could produce specific antibodies for pneumococcal types inoculated as mixtures containing up to 8 different types, he showed that animals immunized with a combination of 3 types gave higher titers for the individual types than did animals receiving 4 to 8 types.

More specific information concerning this synergistic effect of mixed antigens has appeared in recent years. Chen in 1933 had shown<sup>9</sup> that the combination of tetanus toxoid with T.A.B. vaccine had given a better response than is obtained with tetanus toxoid alone. MacLean and Holt in 1940<sup>22</sup> found that this increase was 5 fold. Reference has already been made to

the work of Bell<sup>2a</sup> who reported that a mixture of diphtheria toxoid and pertussis vaccine resulted in fewer failures to immunize than was the case with diphtheria toxoid alone, and that this enhancement of antigenicity was particularly well shown in young infants. Miller and Ryan,<sup>27</sup> using combined aluminum hydroxide adsorbed diphtheria and tetanus toxoids with pertussis vaccine, found a satisfactory response to all components; and the prolongation of a high degree of immunity was very striking in this study, for those retested 2 to 4 years later were all Schick negative and 98% of those tested at this time showed levels of one-tenth unit or more of tetanus antitoxin.

Experiments designed to investigate this synergistic aspect of combined immunization in a quantitative manner are not numerous. Mathieson in 1942 reported<sup>23</sup> that in guinea pigs the antigenicity of diphtheria toxoid was increased by administration in combination with pertussis vaccine. In rabbits, the same product resulted in as good a production of agglutinins for *H. pertussis* as did pertussis vaccine alone. In 1947-48, Greenberg and Fleming described<sup>10a,b</sup> a series of experiments carried out in guinea pigs, of sufficient number and with adequate controls for the constituents of various combinations of antigens, designed to allow for statistical analysis of the results. For example, 4 mixtures of diphtheria toxoid and various concentrations of pertussis vaccine were each inoculated in 3 different amounts and the response to the diphtheria toxoid of each mixture compared with that given by control animals receiving only toxoid of identical strength. The results showed a consistent increase in the immunizing power of the diphtheria toxoid when it is inoculated simultaneously with increasing numbers of *H. pertussis* organisms; and the increased efficiency ranged from 216% to 405% as compared with the controls. The response to diph-

theria toxoid was determined by Schick testing 19 days after a single inoculation. On this basis it could be stated that when the concentration of pertussis organisms usually found in commercial preparations is added to diphtheria toxoid, the immunizing efficiency of the latter is at least doubled. When a third antigen, such as tetanus toxoid or scarlet fever toxin, is added to this combination, the immunizing efficiency of the diphtheria toxoid is increased 5 to 10 fold. As might be expected, the potentiating effect of the presence of other antigens was not demonstrated for the response to pertussis vaccine itself, since that agent is already in a particulate state. Additional studies of the same character carried out in infants<sup>13</sup> confirmed these quantitative results in so far at least as combinations of diphtheria and tetanus toxoids and pertussis vaccine are concerned.

It would seem possible to state that at this time there is general acceptance as to the feasibility and value of combined immunization for prophylaxis against a number of bacterial infections of major importance in all segments of the population. It is also quite certain that a great deal yet remains to be done in order that such procedures may be introduced in a way to confer the greatest possible benefits from their use. Adequately controlled studies must be undertaken to establish size and number of inoculations and to determine the time element that provides for the most effective response to such inoculations. The discovery of antigenic synergy requires further investigation, since it provides a most hopeful indication that smaller dosage will result in a satisfactory immune response and will, at the same time, reduce the possibility of severe reactions in the immunized individual. Further information is needed concerning the advantages and limitations of plain, alum precipitated, and aluminum hydroxide adsorbed products for use in combined form.

The work reported to date has covered such a wide field, and has been carried out under such different conditions, that information on many important aspects of combined immunization is scanty or altogether lacking. This same set of circumstances has made comparison of experimental results very difficult or unsatisfactory. However, the stage of investigation has now been reached where intensive and adequately controlled studies of more limited problems can be undertaken and it is certain that a definite advance in the use of combined bacterial antigens will thereby result.

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# PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 21, 1948

**The Response Pattern of the Pacinian Corpuscle.** DONALD SCOTT, JR., M.D., Ph.D. (Johnson Foundation for Medical Physics, Univ. of Penna.). It is possible to dissect the Pacinian corpuscle in the mesentery of the cat so that electrical records of its activity are easily obtained while it is still receiving its normal circulation. Stimulation of this corpuscle can be effected by means of: (1) a steady pressure of 5 to 30 mg. with a glass rod, or (2) a vibratory stimulus which may be in the form of an audible tone, or (3) a change in the electrolyte balance of the cell fluid by such means as application of isotonic sodium citrate. The response to such stimulation of a single corpuscle is in the form of a series of impulses which are each separated from the next adjacent impulse by an interval which is about 3 to 5 m.secs. in length or some simple multiple thereof. This interval corresponds to that found by Brink in peripheral nerve when treated with isotonic citrate solution and may be regarded as a fundamental oscillatory variation in the excitability of the corpuscle. Careful examination of the record between two impulses separated by several fundamental intervals shows small potentials which appear to be subthreshold electrical changes in the corpuscle having the same fundamental interval as the conducted responses. The length of this interval can be altered by the strength of stimulation: it being shortest when a strong stimulus is applied and the response rate is high. Using a pure tone from an oscillator it is possible to map the response threshold of the corpuscle as it varies with frequency and it is found that there is a sharp "valley" in this curve at a frequency corresponding to the length of

the fundamental interval and a second "valley" at a frequency corresponding to the first harmonic of this fundamental frequency. Using a very strong stimulus it is possible to obtain impulses separated by less than the fundamental interval (in fact these appear to be separated by only the refractory period of the corpuscle) and in this case it appears that with strong stimuli one can produce two responses during a single fundamental interval.

**Do Anesthetics Depress Nerve Cells by Depressing Their Metabolism? Observations on Sympathetic Ganglia.** MARTIN G. LARRABEE, Ph.D. (Johnson Foundation, Univ. of Penna.). Relationships between the effects of anesthetics on the metabolism and on the functioning of nerve cells were investigated by simultaneous measurements of oxygen consumption and synaptic transmission by sympathetic ganglia of rabbits.

A ganglion was excised and placed in flowing solution in a small lucite chamber. Rate of oxygen consumption was determined by measuring with a polarized platinum electrode the rate of fall of oxygen concentration in the chamber when the flow of solution was stopped. Synaptic transmission was measured by the height of the action potential in the postganglionic nerve caused by impulses discharged from ganglion cells in response to volleys of preganglionic nerve impulses.

Chloretone, nembutal, ethyl alcohol, and several higher alcohols were all able to depress oxygen consumption, but this occurred only at concentrations higher than those required to depress synaptic transmission. Ethyl urethane slowed the oxygen consumption by a small amount, the magnitude of which

did not increase as the concentration was raised from levels which did not effect transmission up to those which blocked it. As a control it was shown that rate of oxygen consumption could be considerably reduced by sodium azide without depressing synaptic transmission.

These facts are difficult to reconcile with the hypothesis advanced by others that anesthetics depress the functional capacity of nerve cells by interfering with their metabolism.

**Oximeter Control of the Induced Anoxemia Test of Cardiovascular Function.** RAYMOND PENNEYS, M.D., and CAROLINE BEDELL THOMAS, M.D., (Depts. of Prev. Med. and Med., Johns Hopkins School of Med.). Further experiences with oximeter control of induced anoxemia<sup>1</sup> are presented. Analysis of the inspired gas<sup>2</sup> showed that the oxygen concentration had to be almost constantly altered to maintain a given arterial oxygen saturation. The oxygen concentration necessary to produce a saturation of 75% varied from 8.3 to 12.4%. To keep one particular subject at 80% arterial saturation, for example, 9.5% O<sub>2</sub> was necessary at one moment and, 13.5% O<sub>2</sub> just a few minutes later.

This method of producing a constant arterial oxygen saturation by the administration of a gas of variable O<sub>2</sub> concentration was used in 92 anoxemia tests on 72 normal persons. Practically all subjects could be induced to the desired levels of anoxemia at a standardized rate: 5 minutes from 95 to 80%, 1½ minutes from 80 to 75% or from 75 to 70%. The subject was then maintained at each level for the desired length of time. Blood pressure, pulse and electrocardiogram were taken at

each level. Maximum RS-T change at 80, 75 or 70% was 1 mm. in any one lead or 2 mm. for Leads 1 to 4. The T wave was depressed with progressive lowering of the saturation. The degree of the depression correlated well with the level of saturation. T 3 or 4 was occasionally reversed. No "positive" tests for coronary disease were obtained. The heart rate increased with lowering arterial saturation; the increase was greater and more consistent as 70% was reached. The average systolic and diastolic blood pressure increased slightly at all levels of saturation. The physiological advantages of oximeter controlled anoxemia are discussed.

1. Bull. Johns Hopkins Hosp., 82, 470 1948.

2. In conjunction with Ross L. McLean, M.D., Dept. Med.

**Relation of Number of Metastases to Size, Number and Duration of Primary Tumors. I.** ZEIDMAN, M.D. (Pathology Dept., Univ. of Penna. Med. School). Experiments were designed to determine the effect of primary tumor size, number of tumors, and duration of tumor on the number of metastases. A transplantable fibrosarcoma, T-241, was inoculated into one or both flanks of C-57 mice. Pairs of mice bearing single tumors and pairs bearing double tumors were sacrificed at various intervals between 9 and 26 days after the inoculation of the tumor. The tumor volumes were measured and the lung metastases were counted. There was no significant relationship between number of lung metastases and primary tumor volume or number of primary tumors. The correlation between number of metastases and duration of primary tumor growth was strongly positive.

# BOOK REVIEWS AND NOTICES

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## THE DIGESTIVE TRACT IN ROENTGENOLOGY.

By JACOB BUCKSTEIN, M.D., Ass't Prof. of Clinical Medicine, Cornell Univ. Med. Coll. Pp. 889; 1030 ills. Phila.: J. B. Lippincott, 1948. Price, \$16.00.

THIS book is one of the best that I have had an opportunity to review. The author, in his first book, did a magnificent piece of work and in this instance he has improved on it in many ways. Most of the commonly known facts concerning the gastro-intestinal tract are discussed as well as many of the rare conditions. This book is the type of book that should be on the desk of every radiologist and every gastro-enterologist. Many of those interested in general medicine will find it informative.

The reviewer has only one suggestion—that a chapter on the technique of fluoroscopy and radiography as it concerns the gastro-enterologist be included in further editions. In this detailed comments on protection of the patient and of the operator from over-exposure should be included. A book such as this one will have wide use and many people will attempt to do fluoroscopy who are not adequately informed about its dangers. The print is excellent and the illustrations are good.

E. P.

## DRUG RESEARCH AND DEVELOPMENT. Edited

by AUSTIN SMITH, M.D., Director, Division of Therapy and Research, American Medical Association, and ARTHUR D. HERRICK, Food and Drug Consultant, Attorney, and Author. Pp. 608. New York: Revere, 1948. Price, \$10.00.

TODAY few persons interested in the development of drug therapy have a clear picture of the operations involved in formulating, testing and marketing a new formula. To make available a reasonably detailed survey of these steps in drug research and development, the editors of this volume have called upon their own knowledge and that of 16 other recognized experts in fields ranging from pharmacology through patent and trademark law to advertising and price maintenance. For example, M. L. Tainter presents in 33 pages an excellent discussion of laboratory research, including purpose, objectives and general plan of organization, the types of research and development and an able defense of the use of animals in research.

At the other end of the line, C. S. Downs explains in 42 pages the objectives of advertising, the media used (sample, direct mail, and professional journals), the methods of

determining proper appropriations, and other lesser aspects.

The authors are to be complimented for the manner in which they have presented the over-all picture of each topic as well as brief discussions of its most important procedures and problems. Their success can be attributed to their conscientious avoidance of generalities. The book is enthusiastically recommended to anyone desiring a balanced background in the many operations which make a modern drug available to the physician.

F. B.

## SYMPOSIA ON NUTRITION. Vol. I. NUTRITIONAL

ANEMIA. Edited by ARTHUR LEJWA. Pp. 194. Illustrated. Cincinnati, Ohio: Robert Gould Research Foundation, 1947. Free. on request.

THIS volume comprises a brief preface by the Editor, Introductory remarks by E. V. McCollum and chapters by Wintrobe, Elvehjem, Darby, Zuelzer, Schultze, Cartwright, Moore, Guest, Sebrell and Vilter each representing a contribution to a Symposium on Nutritional Anemia organized by the Gould Foundation and held in Cincinnati under auspices of The College of Medicine of the University of Cincinnati in October 1947. It is an excellent summary of the known data at that time. The symposium was presented a few months too soon to include notice of "B-12" which constitutes an important new chapter for the next edition. This little volume is unreservedly recommended to all "individuals and organizations interested in nutritional problems" and especially to all students of clinical hematology.

T. F., Jr.

DEEP ANALYSIS. By CHARLES BERG, M.D. (Lond.), D.P.M. Pp. 254. New York: W. W. Norton, 1947. Price, \$3.50.

DEEP ANALYSIS is a brave attempt. However, it falls far short of success. The author does not reveal what moved him to write this book. The jacket "blurb", however, affirms that being dissatisfied with the short case descriptions which abound in psychiatric literature, he undertook to write "a complete Freudian analysis of a single case." The term "complete" is in this instance both tricky and frustrating, for the book is most certainly not complete (i.e. fully adequate), either as a case record, or as an exposition of "what goes on" between analyst and patient. Time and again the author writes, as indeed he could not but write, "space will not admit . . . complete exposition;" "space will not permit



a recital of . . ."; "many excellent dreams and their associations will have to be omitted." And toward the end is to be found this frank admission: "Notwithstanding all the care and compendiousness of our transcription of this analysis, as we have not ourselves been able to experience emotionally what the patient under analysis experienced, we remain infinitely short of a true revelation of the daily, hourly, minutely details in all their voluminousness—details which the subject of analysis alone can emotionally experience, and in which alone can lie the appreciation of something as indescribable as life itself" (p. 230).

In this rather long and poorly constructed sentence the author confirms what Freud said more succinctly: "It does not lend itself to demonstration". "One learns it on 'one's own hide'".

*Deep Analysis* is a brave attempt, because, even though unsuccessful, it tried to do what to my knowledge no other author has attempted, and that is to reveal the dynamics of treatment and recovery in a given case. That is a much more difficult task than to describe in general terms the *theory* of psychotherapy. To be effective in such an effort the descriptive encompassment would need to embrace the therapist as well as the pathology and the patient. That means that the writer of such a book would have to "get behind" both, the therapist and the patient, and externalize his appreciation of what he does to and with the patient (and vice versa) and why. Most orthodox analysts—and Dr. Berg appears to be strictly orthodox—find such a task difficult, if not impossible. Hence Dr. Berg's confession: "In some of our apparently most successful cases analyst as well as patient are both befogged as to the mechanism which produced results which were beyond their dreams" (p. 229). I. G.

**ADVANCES IN BIOLOGICAL AND MEDICAL PHYSICS.** Vol. I. Edited by JOHN H. LAWRENCE and J. G. HAMILTON, Division of Medical Physics, Univ. of California. Pp. 484. Illustrated. New York: Academic Press, 1948. Price, \$8.60.

This text consists of a series of articles on various aspects of radioactivity, written by some of the foremost research workers in the field. Among numerous topics considered are the use of isotopes in clinical and experimental medicine, the physics of radioactivity, results of *in vivo* studies on metabolism with nitrogen and carbon isotopes, instruments used in detection of radioactivity, and recent discoveries made by the use of radioactive phosphorus, iron, and iodine. Also included are chapters devoted to radiation protection, and effects of the atom bomb on the Japanese.

Each topic is carefully and thoroughly expounded, and many new developments are described and correlated. I. Z.

#### AN INTRODUCTION TO MEDICAL MYCOLOGY.

By GEORGE M. LEWIS, M.D., and MARY E. HOPPER, M.S., Cornell Univ. 3d edition. Pp. 336; 103 ills. Chicago: Year Book Publishers, 1948. Price, \$8.50.

IN LESS than 10 years, this book has gone through 3 editions. Like its predecessors, the first part deals with the clinical, theoretical, and experimental phases of the subject, and the second part outlines pertinent laboratory procedures. This volume is a few pages longer than the second and contains more illustrations. Its format retains the good qualities of the preceding editions; the price, however, is higher. It is suggested that bold face headings would help the reader in locating the material presented and illustrations of the reproductive forms of fungi would help to clarify the later illustrations for the novice.

This is still the most practical volume in English available to the dermatologist who is not a specialist in mycology. H. B.

#### AN INTRODUCTION TO THE HISTORY OF DENTISTRY.

By BERNHARD WOLF WEINBERGER, D.D.S., Prof. of Dental History and Literature, New York College of Dentistry. In 2 vols. Pp. 514 and 408; 177 and 136 ills. St. Louis: C. V. Mosby, 1948. Price, \$20.00.

THESE volumes are separate though related works. In the first, Dr. Weinberger considers dentistry from its earliest period to the end of the 18th century. The second is concerned with dentistry in America from 1620 to the middle of the 19th century. Dr. Weinberger's collection of dental bibliographical and historical material is probably the most complete in existence. This and many other sources have been tapped for the numerous reproductions of original title pages, dental advertisements, wood cuts, et cetera, which depict the gradually accumulating knowledge of dental anatomy, physiology, pathology and therapy.

The beginnings of dentistry are lost in the obscurity of prehistoric man. Nevertheless, that dental problems existed is indicated by examination of skulls and teeth which have been recovered by archeologists. Not only are fractured teeth and jaws found but also unerupted and malposed teeth. Caries of the teeth was not so rare among primitive peoples as is commonly reported. The relief of pain from toothache led to the knocking out of teeth and eventually to more refined methods of extraction. The replacement of lost teeth by natural or artificial substitutes was a next step. Gold castings cemented into the teeth were used by South American Indians for

adornment centuries before metals were used for the treatment of dental caries. All this and much more is woven into a background of the history, folklore, medical theory and practice of many races of people down through the Middle Ages to the Renaissance and the beginnings of the biological sciences upon which the practice of modern medicine and dentistry is based. In the final section of the first volume the rise of dentistry as an independent profession and the coincidental growth of dental literature is described.

The development of dentistry in America is documented in greater detail. There are chapters on early dentists including Paul Revere. Other chapters are concerned with George Washington from the point of view of his numerous dental difficulties, and of Charles Wilson Peale, the artist, who was led to the manufacture of porcelain teeth in order to restore a more natural appearance to the face of his distinguished client, Washington. Much material of an incidental historical interest is included.

There are indices of personal names as well as of subject matter. These books are a most valuable contribution to the history of dentistry. P. B.

**MIDWIFERY.** By TEN TEACHERS, under the direction of CLIFFORD WHITE. 8th ed. Pp. 560; 217 ills. Balt.: Williams & Wilkins, 1948. Price, \$6.00.

THIS condensed text has had a well-merited popularity extending over a period of 30 years. Emphasis is placed on the practical side of the subject. Exposition is logically planned and coordinated. The style is uniformly lucid and concise. In this edition, 3 of the original "teachers" have yielded to younger successors. C. B.

**THE CLINICAL APPLICATION OF PSYCHOLOGICAL TESTS.** By ROY SCHAFER, M.D. Menninger Foundation Monograph Series No. 6. Pp. 346. New York: International Universities Press, 1948. Price, \$6.75.

WORKERS in individual adjustment will find much of interest in this Monograph. From the method of presenting the performance on a series of psychological tests by patients suffering from different types of mental illness, rounded pictures of the different pathological syndromes emerge, illustrating characteristic thought and affective processes in each type of illness.

The first third of the book develops diagnostic summaries of 11 pathological states and several sub-classes. The diagnostic summaries, as well as the case studies which constitute the last two-thirds of the book, are based upon the psychological tests now used at the Menninger Foundation.

Ten minutely detailed and 10 more briefly summarized case reports form a valuable ad-

dition to the collections of cases already available in the standard works of Klopfer, Beck and Murray.

Mr. Schafer's work is careful and timely. It will be useful both as a reference volume and as a teaching medium. R. C.

## NEW BOOKS

**A.M.A. Interns' Manual.** By THE AMERICAN MEDICAL ASSOCIATION. Pp. 209. Phila.: W. B. Saunders, 1948. Price, \$2.25.

Prepared by several of the Councils of the A.M.A., this book is designed to help orient the intern in his hospital duties. There are 9 sections: information relative to internships and residencies; clinical and laboratory data; drug administration; useful drugs; treatment of poisoning; diet and nutrition; physical medicine; legal aspects of internship; organization of the American Medical Association. C. R.

**The Autobiography of Benjamin Rush, His Travels Through Life together with his Commonplace Book for 1789-1813.** Edited by GEORGE W. CONNER for the American Philosophical Society. Pp. 399; 13 ills. Princeton, N. J.: Princeton Univ. Press, 1948. Price, \$6.00.

The "Travels Through Life, an account of sundry incidents . . . written for the use of his children", covers up to 1800, thirteen years before his death. The random notes of the Commonplace Books, or diaries, are equally revealing of this observant, vivid and complex personality. No small part of the value of this careful compilation by a well known writer on medical history is to be found in the Introduction, the 4 Appendices, and the copious footnotes and editorial comments. E. K.

**Fundamentals of Psychoanalysis.** By FRANZ ALEXANDER, M.D., Clinical Prof. of Psychiatry, Univ. of Illinois. Pp. 312. New York: W. W. Norton, 1948. Price, \$3.75.

This book replaces, naturally with many changes, part of the author's "The Medical Value of Psychoanalysis", the 2d edition of which appeared 11 years ago. Its main object is "a comprehensive presentation of fundamental theory and its application to treatment."

**The Clinical Management of Varicose Veins.** By DAVID WOOLFOLK BARROW, M.D. Pp. 155; 58 ills. New York: Paul B. Hoeber, 1948. Price, \$5.00.

On a basis of some 2500 observations on patients or their records, the author builds a dynamic picture of the development of varicose veins, their complications and how they should be treated.

*Mineral Nutrition of Plants and Animals.* By FRANK A. GILBERT, Ph.D. Pp. 131. Illustrated. Norman: University of Oklahoma Press, 1948. Price, \$2.75.

*Health Progress, 1936 to 1945. A Supplement to 25 Years of Health Progress.* By LOUIS I. DUBLIN, Ph.D. Pp. 147. New York: Metropolitan Life Insurance Company, 1948. No price.

*Liver Injury.* Transactions of the 7th Conference, January 15, 16, 1948. Pp. 95; 15 ills. Price, \$1.50. *Blood Clotting and Allied Problems.* Transactions of the 1st Conference, Feb. 16-17, 1948. Pp. 179. Price, \$3.25. *Factors Regulating Blood Pressure.* Transactions of the 2nd Conference, Jan. 8-9, 1948. Frank Fremont-Smith, Medical Director. Pp. 170. Illustrated. New York: Josiah Macy, Jr. Foundation. Price, \$2.75.

*A Doctor Talks to Teen-Agers.* By WILLIAM S. SADLER, M.D., F.A.P.A., Consulting Psychiatrist, Chicago. Pp. 379. St. Louis: C. V. Mosby, 1948. Price, \$4.00.

This book, based on the author's experience and "directed personally to young folks", contains considerable information of practical, theoretical and idealistic nature that will be found useful and perhaps inspiring, not only to teen-agers themselves, but to physicians, parents, and others who are concerned with understanding and counselling young people.

W. F.

## NEW EDITIONS

*Diabetic Manual.* By ELLIOTT P. JOSLIN, M.D., Sc.D., Clinical Prof. of Medicine, Emeritus, Harvard Medical School. 8th ed. Pp. 260; 51 ills. Phila.: Lea & Febiger, 1948. Price, \$2.50.

*Textbook of Anaesthetics.* By R. J. MINNITT, M.D., Royal Liverpool United Hospital, and JOHN GILLIES, M.C., Univ. of Edinburgh. 7th ed. Pp. 568; 229 ills. Balt.: Williams & Wilkins, 1948. Price, \$8.00.

This book continues to increase in size—80 more pages in this edition. New material is presented on the medico-legal aspects of anesthesia, curare and regional anesthesia. There is a good bit of useful information available.

R. D.

*Control of Pain in Childbirth.* By CLIFFORD B. LULL, M.D., and ROBERT A. HINGSON, M.D. Introduction by Norris W. Vaux, M.D. 3d. ed. Pp. 522; 170 figs. Phila.: J. B. Lippincott, 1948. Price, \$12.00.

*Outline of Histology.* By MARGARET M. HOSKINS, Ph.D., and GERRIT BEVELANDER, Ph.D., New York Univ. 2d ed. Pp. 112; 56 ills. St. Louis: C. V. Mosby, 1948. Price, \$3.50.

*An Introduction to Materia Medica and Pharmacology.* By ELSIE E. KRUG, R.N., M.A., and HUGH ALISTER MCGUIGAN, Ph.D., M.D. 5th ed. Pp. 558; 37 ills., 15 color plates. St. Louis: C. V. Mosby, 1948. Price, \$4.00.

A useful book especially designed for student nurses.

*Organic Chemistry.* By ELDIN V. LYNN, Ph.D., Prof. of Chemistry, Massachusetts College of Pharmacy. 3d ed. Pp. 355. Phila.: Lea & Febiger, 1948. Price, \$5.00.

*Diseases of the Adrenals.* By LOUIS J. SOFFER, M.D., Asst. Clinical Prof. of Medicine, Columbia Univ. 2d ed. Pp. 320; 45 ills., 3 color plates. Phila.: Lea & Febiger, 1948. Price, \$6.50.

This book is an interesting and concise monograph, dealing with all aspects of the adrenals but with emphasis on the clinical manifestations of adrenal disease. The new material in this edition includes the clinical and experimental data on pituitary-adrenocortical function which have been accumulated in various medical centers during the last few years!

I. Z.

*An Introduction to Gastro-Enterology.* By WALTER C. ALVAREZ, M.D., Prof. of Medicine, Univ. of Minnesota. 4th ed. Pp. 903; 269 ills. New York: Paul B. Hoeber, 1948. Price, \$12.50.

This edition (2d under its new title) represents an improvement over the 3d in that it includes many additions to the sections on intestinal innervation, the functions of the colon and flatulence; also it covers adequately the subjects of electro-enterograms and vagotomy. The text, like that of all Alvarez' writings, is easy to read, and many excellent illustrations are included. The physiological discussions of many gastro-intestinal problems are clear and convincing. An extensive bibliography of about 2800 references adds greatly to its value. It will be found particularly helpful to those investigators in gastro-enterology who need a reference guide to the important literature.

J. H.

*Principles and Practice of Ophthalmic Surgery.* By EDMUND B. SPAETH, M.D., Prof. of Ophthalmology, Graduate School of Medicine, Univ. of Penna. 4th ed. Pp. 1044; 649 ills., 8 color plates. Phila.: Lea & Febiger, 1948. Price, \$15.00.

THIS first post-war edition of what has already been called in these columns the best book on the subject in the English language contains much new material on, *inter alia*, plastic surgery, plastic enucleation, paralytic squint, exophthalmos, radium therapy and similar subjects. It is 110 pages larger than the 3d edition (1944). Its high standards of breadth of scope and clarity of text, excellent illustrations, and good bookmaking are well maintained.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1949

## ORIGINAL ARTICLES

### WHY ARE FEVER TEMPERATURES OVER 106° F. RARE?\*

BY EUGENE F. DuBOIS, M.D.  
NEW YORK, NEW YORK

(From the Department of Physiology, Cornell University Medical College, and the Russell Sage Institute of Pathology in affiliation with The New York Hospital)

THERE is difficulty in considering high temperature by itself because it is so closely associated with the symptoms of infection. As a rule the highest readings are found in the most severe stages of the worst fevers. They are accompanied by all the manifestations of toxemia acting upon a patient weakened by partial starvation.

High temperature in itself can damage tissues but it is hard to estimate the level at which each particular organ is injured. Exceptional patients have survived temperatures of 113° F. (45° C.) but there are not many who live more than a few days or weeks after the temperature has reached 107° F. (41.7° C.). We know from the work of fever therapists that persons in good condition can stand 107.6° F. (42° C.) for periods of 8 to 10 hours but this is close to the upper limit of tolerance. Temperatures within 2 degrees of this danger level are seldom found in fever. Why are readings of 106° F. rare?

The facts at our command can be best explained by assuming that the temperature regulating mechanism functions well at the higher thermostat level set by the particular dis-

ease. There must be an emergency mechanism that strongly resists the approach to levels that threaten life.

Moderately high temperature around 104° F. (40° C.) cannot be regarded as dangerous or even deleterious, inasmuch as it is the level found in athletes during hard exercise. Muscles are most efficient at this temperature. Patients in good condition adjust themselves well to moderate fever. We noted this in the old days in Bellevue Hospital when there were still many typhoid patients. If they were able to take a well balanced, high-calory diet they were so clear mentally that with temperatures of 104° F. they sat propped up in bed reading the newspaper every morning.

There is still much to be learned about temperature regulation in health and even more to be learned about fever. We are quite ignorant regarding the details of the chemical, electrical and physical reactions which occur in the hypothalamus and skin in response to changes in temperature. It is by delicate adjustments in these tissues that the balance between heat loss and heat production is maintained. We know little about the causation of fever

\*Thirty-first Mellon Lecture presented before the Society for Biological Research, School of Medicine, University of Pittsburgh, May 27, 1948.

and the manner in which fever producing substances affect the level of thermostatic control. A study of high fever may throw light on this control.

There is an extensive literature on temperature regulation reviewed by Thauer<sup>9</sup> and by Ranson and Magoun.<sup>7,8</sup> In a recent small monograph on fever, DuBois<sup>3</sup> has published 2 graphs indicating the limits of body temperature. The first gives the range found in normal persons with a lower limit of 96° F. (35° C.) for early morning in cold weather and an upper limit of

upper safe limits of body temperature. Most mammals have temperatures between 97 and 102° F. with upper safe limit of 107 to 110° F. Birds with more labile normal, 105 to 107° F., have an upper safe limit of 113° F. Lee speaks of the considerable species difference with little obvious evolutionary plan and no high correlation of normal with upper lethal body temperature.

In an article on body temperature prepared in 1939 DuBois<sup>2</sup> recorded the rectal temperature readings of 100 unselected patients in the medical wards

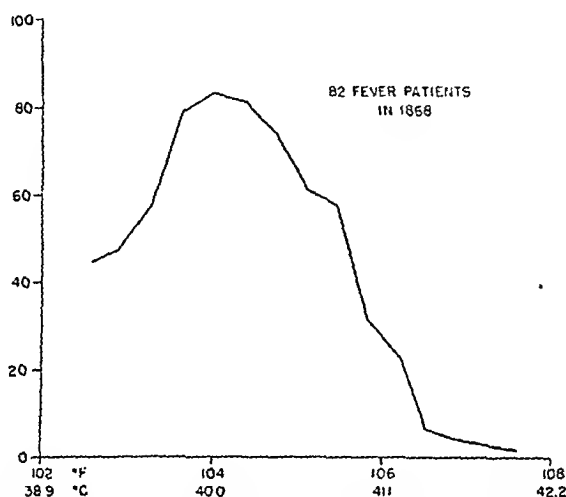


FIG. 1.—All the axillary temperature readings above 39° C. in the 82 fever charts in the appendix to Wunderlich's book on *The Temperature in Diseases*, 1871. The ordinates give the number of readings at each level of temperature.

104° F. (40° C.) for the rectal temperature of athletes after hard exercise. In the second graph he has tried to show the limits of human survival. The lower limit is about 74° F. (23° C.) and the upper about 113° F. (45° C.). Only a few persons have survived at these extremes. The safe upper limit of temperature for persons in good condition has been closely approached by the fever therapists when they deliberately maintain temperatures of 42° C. (107.6° F.) for 8 or even 10 hours.

Lee<sup>6</sup> in an excellent review of heat and cold has described the normal temperatures of homeotherms and the

of The New York Hospital. None was above 105° F. (40.5° C.) and none below 96.8° F. (36° C.). He suggested that there was a secondary regulation of temperature at about the level of 105 to 106° F. In a similar study made in 1948 it was obviously unfair to use the 1948 ward patients. The formerly well established fever courses of many diseases have been so distorted by sulfanilamides, penicillin and streptomycin that they are almost unrecognizable. It was therefore necessary to go back to the older literature and to the record of patients in the New York Hospital before 1932.

In making the analysis care was taken to omit all readings influenced by cold baths, cold sponges, serums or by intravenous injections that might have contained pyrogens. It was also necessary to omit all readings in the last 2 days of life because temperature regulation is seriously impaired in moribund patients. Cases of heat stroke were placed in a special category. Only readings above 39° C. (102.2° F.) were recorded.

One of the best studies of fever is the classical book of Wunderlich<sup>10</sup> published in 1868 and translated into English in 1871. The clinical thermometer had only just been introduced

with malaria admitted to the New York Hospital before 1932 (Fig. 2). Twenty-five patients were studied who had been given malarial fever therapy in the same hospital between 1932 and 1948. Inasmuch as relapsing fever has the reputation of giving the highest temperatures, the literature was searched and the readings in 50 cases of various types of this disease were recorded in a separate graph.

There was a marked similarity in the temperature distribution curves of these diseases of widely different etiology. The greatest number of readings, the peaks of the curves, came between 40.0° and 40.8° C. Tempera-

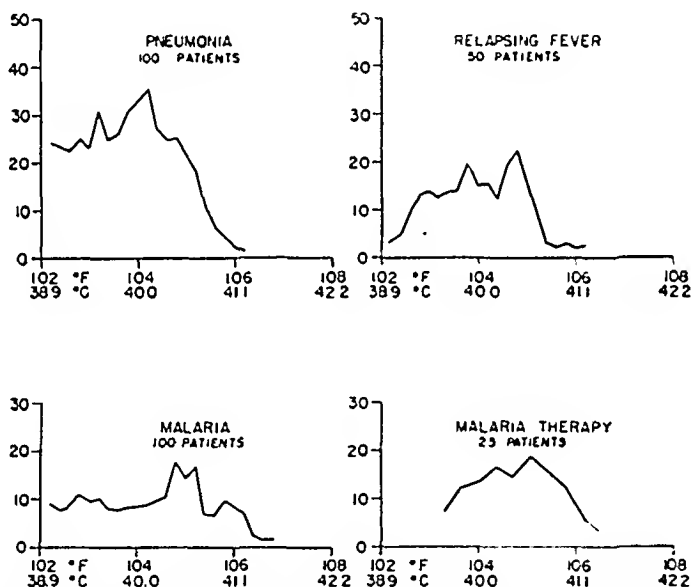


FIG. 2.—Rectal temperature readings in 4 different fevers. Ordinates give the number of readings at each level of temperature.

and there was so much enthusiasm for the new instrument that the physicians themselves made the readings. They measured axillary temperatures, which in high fevers are very close to rectal readings. Fortunately Wunderlich in the appendix to his book gives the charts of 82 patients with high fevers including typhoid, typhus, pneumonia, and the exanthemata. Fig. 1 charts all his readings above 39° C. (102.2° F.).

Similar graphs were made for 100 patients with lobar pneumonia and 100

tures above 106° F. (41.1° C.) were rare. This point was brought out even more clearly in Figures 3 and 4. In 1761 readings, only 75 were above 106° F. There must be an automatic cut-off that stops the rise of temperature before it reaches the level where high temperature itself becomes a menace to life.

The fact that there were 608 readings between 104 and 105° F. (40.0°-40.6° C.) and less than half as many between 102 and 103° F. was unexpected. The shape of the curve indi-

cates that in these particular high fevers the thermostatic control was set in the neighborhood of 104 and 105° until defervescence was well established. Of course the shape of the curve would have been very different if the milder infections such as bronchitis, chicken pox and influenza had been included.

In examining the records it was obvious that there is a tendency to place the dot on the full degrees more

valleys of hospital temperature charts are artefacts. When we study fever patients in the Sage respiration calorimeter and make readings every 4 minutes with electrical thermometers the curves are smooth and rounded.

The respiration calorimeter has also brought out the fact that there is no one body temperature and that it is impossible to determine accurately an average body temperature. The highest temperature is found in the liver or in

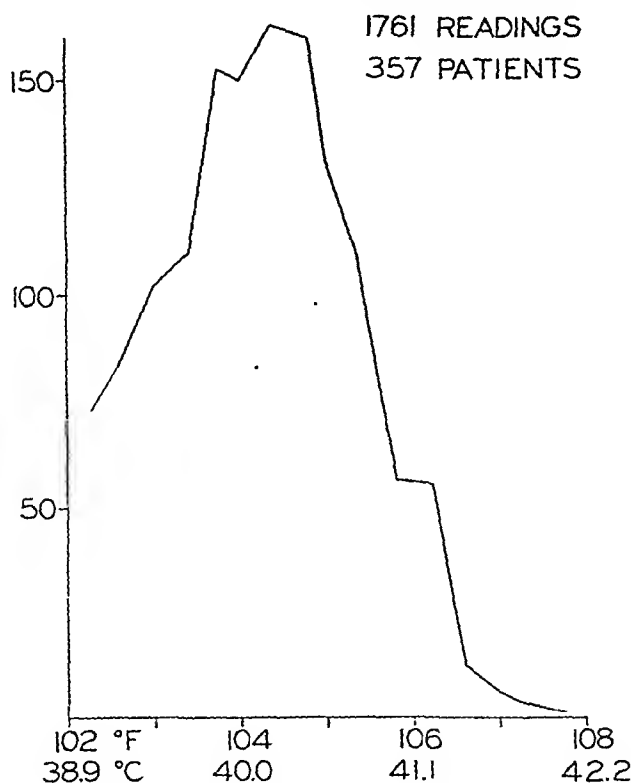


FIG. 3.—The readings of Figs. 1 and 2 combined.

often than on the nearest fractions. For example the number of recordings at 40.0° C. greatly exceeded those at 38.8 or 40.2°. Therefore the curves were smoothed by averaging with each column the readings of its right hand and left hand neighbors. It must also be realized that when measurements are made every 4 or even every 2 hours some of the highest and lowest points are missed. The sharp peaks and

the muscles in the case of severe work. The rectal temperature averages about 1° F. below that of the liver, the oral temperature another degree lower. The skin and subcutaneous tissue may be 2 to 3° lower in a warm environment or more than 60° F. lower in a cold environment. About one-fifth of the body substance lies within 1 cm. of the surface and its temperature changes are best indicated by skin readings.

The rectal readings usually indicate the changes in about 80% of the body mass. These percentages vary with the environment and when the skin is really cold the gradient penetrates much deeper than a centimeter. Under these conditions the temperature changes of about one-half the body mass are best indicated by changes in skin temperature. At the other extreme, in fever, the blood is cooled near the surface and the subcutaneous temperature is close to the rectal.

During a chill with relative cooling of the surface and rapid rise of rectal temperature the superficial and internal masses of the body change at different

pothalamus which most authorities believe to be the region of the temperature regulating mechanism. The question that concerns us now is the existence of a mechanism in febrile disease that prevents the body temperature from rising above 106° F.

Were it not for such a mechanism the body temperature could rise from 40 to 43° C. just as easily and rapidly as it rises from 37 to 40° C. There is no physical reason to prevent the body temperature from shooting up to 44° C. (111° F.) or higher. It only requires a storage of 60 calories to raise the average man's temperature 1 degree Centigrade. During a severe chill a man can

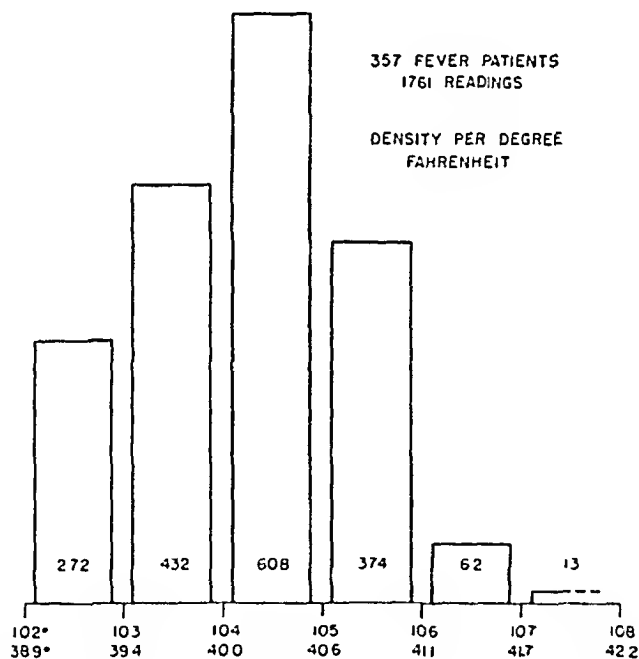


FIG. 4—The readings of FIGS. 1 and 2 combined in a density chart per degree Fahrenheit

rates and often in different directions. In severe exercise also the skin temperature falls while the rectal temperature rises. It is obvious that in some conditions heat may be transferred from one part of the body to another without significant alteration in the overall temperature of the body mass.

Bearing in mind these limitations we still have in the graphs a fairly accurate picture of the highest temperatures of the internal organs including the hy-

pothalamus which most authorities believe to be the region of the temperature regulating mechanism. The question that concerns us now is the existence of a mechanism in febrile disease that prevents the body temperature from rising above 106° F.

store more than 200 calories an hour. With severe exercise an athlete can store this amount in a few minutes. High body temperature is accompanied by an increase in basal metabolism and patients with fever temperatures of 40° C. exhibit heat productions of about 40% above the normal. This may be augmented by restlessness or even delirium. The rise is partially compensated by an increased radiation and convection as the temperature of



the skin rises more and more above that of the environment. For example, if the temperature of the air and walls of the hospital ward be 20° C. (68° F.) and the patient's rectal temperature 40° C., skin temperature 38° C., there would be a gradient of 18° C. between skin and air. If his rectal temperature were 44° C. and skin temperature 42° the gradient would be 22° C. It is doubtful if this 4 degree difference is significant in comparison with the major channel of heat loss, vaporization. If it were important we would find fever temperatures 5 or 10 degrees higher on hot summer days than they are in winter.

There are several special conditions in which body temperatures do exceed 41° C. The best known is fever therapy. If the patient is put in a cabinet and heat loss through the skin prevented, the body temperature will rise progressively. If extra heat is poured into the body, temperatures will rise rapidly to any desired level. Occasionally it gets out of control and the rise continues after the patient has been removed from the fever cabinet.

A second well known cause of marked hyperthermia is heat stroke. No attempt will be made to review the extensive literature on this subject but attention is called to the excellent study of Ferris, Blankenhorn, Robinson and Cullen<sup>4</sup> who have described in great detail 44 cases of heat stroke in Cincinnati in the hot spell of 1936. Most of the patients were brought to the hospital after 3 days of intensely warm weather, few had been exposed to much direct sunlight. Those with admission temperatures over 106.8° F. were comatose or delirious. It so happened that all with temperatures under 107° F. (41.7° C.) ultimately survived and that a few with temperatures at the top of the clinical thermometer failed to die. Many of the patients reported that a few hours before they were prostrated they had noticed that

sweating stopped. All of them on admission had hot, dry skins.

Several other reports of heat prostration have recorded that all of the skins were hot and dry. A few have described some patients with moist skins but these may have been cases of heat exhaustion which differs from heat stroke in that it resembles shock with failure of the peripheral circulation and with a normal or only slightly elevated temperature.

It is difficult to see how a man who can sweat normally could possibly develop heat stroke except in conditions of high humidity. Blum<sup>1</sup> estimates that soldiers marching in the desert increase their metabolism up to 265 calories an hour, 4 times the basal level, and in addition they may receive from the direct sunlight, reflected heat and hot air an additional load of over 200 calories an hour. They gain heat through radiation and convection and the only channel of loss is vaporization. This rises to adequate high levels. The men vaporize 1 to 1½ liters of water an hour and each liter vaporized takes care of about 585 calories. Similar results have been obtained in carefully controlled laboratory experiments. When, however, the humidity is high as it would be in a jungle, vaporization becomes less effective and under the stress of heavy work the internal temperature rises to 103° F. or higher until work becomes impossible.

If under long continued stress there is finally an exhaustion of the sweat glands the body temperature rises with great rapidity. A few studies of fatigue of sweat glands have been described by Lee<sup>6</sup>, and by Gerking and Robinson<sup>7</sup> who observed a group of healthy, well acclimated soldiers walking on a treadmill in a hot room. They were kept in water and salt balance by drinking 0.1% saline solution. In the first 2 hours of work the average rate of sweating was 1400 gm. per hr. and the sweating rates declined from 10 to 80% of this

value by the 6th hour. They conclude that the sweating mechanism was fatigued though not exhausted. Apparently this is not often the result of dehydration or lack of salt. It is very different from the blockage of sweat glands by keratinization of their orifices as observed recently in the Pacific Area.

A third condition that exhibits temperatures above 106° F. (41.1° C.) is the moribund state a few hours before exitus. Usually in fevers the temperature mounts to high levels just before death. Sometimes it remains flat, sometimes it falls. In the last hours of life there is a failing of circulation and impairment of the temperature regulating mechanism.

A great deal has been written about abnormally high temperatures in brain injuries or tumors involving the hypothalamic region. From a limited study of many cases reported in the literature there is no evidence that the temperatures differ markedly from those found in infectious diseases. Probably the hyperthermias that have impressed clinicians are the terminal high temperatures of moribund patients.

Under certain special conditions it is possible to obtain very high temperatures in fever. If intravenous injections which happen to contain pyrogens are given to fever patients the results may be dramatic. I remember one such case when in 1921 at Bellevue Hospital Cecil and Larsen were treating lobar pneumonia with an antibody solution that caused a significant reduction in the mortality. In spite of every precaution known at that time an occasional batch would contain pyrogens. One poor patient after an intravenous injection had such a violent chill that the clinical thermometer rose to 110° F. and burst. The laboratory thermometer showed that his rectal temperature was 112° F. (44.4° C.). Prompt application of cold water reduced the fever rapidly and much to our surprise the patient recovered.

Summarizing these special conditions in which temperatures over 106° F. (41.1° C.) are found, the following classification can be made: (1) A sudden overwhelming heat load, as in a fever cabinet or the chill from pyrogens. (2) A prolonged overwhelming load with exhaustion of the sweat glands as in heat stroke. (3) Failure of the circulation and, or, failure of the temperature regulating mechanism in moribund patients. (4) Some infectious diseases with occasional readings between 41 and 42° C. These represent the scatter which is usually found at the edges of bell-shaped Gaussian curves of distribution.

Thus it is evident that in fevers the great majority of readings are lower than 106° F. which is safely below the point at which temperature itself is dangerous. Everything points to a temperature regulating mechanism that functions well at the thermostatic level set by the particular stage of the disease. Presumably this is located in the same centers in the hypothalamus that control temperature in health and respond grossly to changes in the blood and more delicately to changes in the skin. The sharp limitation of temperatures at the level of about 106° F. points toward an "emergency regulatory mechanism in fever" that protects the body with great efficiency.

This mechanism can do but little in the way of reducing heat production unless it sends the patient into a quiet coma. It cannot do much through increased radiation or convection but can do a great deal by increased peripheral circulation and particularly by increased sweating.

The patient can help if he is strong enough to throw off his blankets. The nurse can cool the room. The doctor can follow the custom of aiding nature's vaporization by ordering cool sponges with water or dilute alcohol. The important thing is to cool as much blood as possible in the subcutaneous

tissues. Too great a chilling of the skin might lead to constriction of the peripheral blood vessels and diminished cooling of the internal organs. There is also the possibility that chilling of the skin might start signals to the temperature regulating center that would produce an effect exactly the opposite of that which was desired.

Drinking cool water is comforting but relatively inefficient in reducing temperature. For example if a patient could possibly swallow a liter of water at zero Centigrade it would abstract 40 calories, enough to lower his temperature only 2/3 degree. This same water vaporized from his skin would abstract 585 calories.

**Summary and Conclusions.** 1. A survey has been made of 1761 temperature readings in 357 patients suffering from diseases characterized by high fever. Only 4.3% of the temperatures were above 106° F. (41.1° C.). None was above 107.8° F. (42° C.).

2. In these particular fevers 608 readings came between 104 and 105° F. (40.0 to 40.6° C.). Less than half as many fell between 102 and 103° F. (38.9 to 39.4° C.). These are indications that in these fevers the "thermostat level" for the temperature regulating mechanism was set in the neighborhood of 104 to 105° F.

3. Human temperatures much higher than 106° F. can be found in several conditions other than infectious diseases. The normal temperature regulating mechanism may be overwhelmed suddenly by a fever cabinet or gradually by heat stroke with its exhaustion of the sweat glands. The mechanism together with the peripheral circulation often fails in moribund patients.

4. Except for these anomalous conditions temperatures are kept safely below the danger level by an "emergency regulatory mechanism in fever" which acts chiefly through the peripheral circulation and the sweat glands.

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# MAJOR SURGICAL OPERATIONS IN THE PRESENCE OF BUNDLE BRANCH BLOCK

## A STUDY OF THE OPERATIVE RISK IN 59 PATIENTS

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TABULATIONS of the operative mortality, cardiac complications and other postoperative complications in 59 patients with bundle branch block (BBB) subjected to major surgical operations at Memorial Hospital suggest that such patients withstand operation almost as well as patients of the same age group who have normal electrocardiograms. The presence of BBB has been regarded by some as a contraindication to the performance of all but emergency surgical procedures because of the danger of ventricular standstill or ventricular fibrillation.<sup>1</sup> This attitude is encouraged by studies stating that the average life expectancy associated with this electrocardiographic finding is 2 years.<sup>3,6</sup> A more recent survey, however, has shown that 42% of the 50 cases of BBB were still living 8 years and 2 months after the condition had been diagnosed.<sup>1</sup>

Bundle branch block in the aged is almost always associated with arteriosclerotic heart disease, although it may occur with rheumatic, syphilitic or congenital forms of heart disease. Any elderly patient who must undergo major surgery should have a careful preoperative evaluation of his cardio-vascular status; but our data do not support the contention that BBB *per se* constitutes a major contraindication to surgery. Other factors, such as the presence of cardiac hypertrophy, congestive failure, a history of recent myocardial infarct

appear to us to be of far more importance than the presence of a single electrocardiographic abnormality. All these criteria must be evaluated if the internist is to give an intelligent estimation of the operative risk. Increasing knowledge of pre- and postoperative care, perfected techniques of anesthesia, and the introduction of antibiotics have combined to make the prognosis for patients with heart disease undergoing major surgery much less formidable.

Cancer is invariably a fatal disease in the absence of treatment and, moreover, its course in the untreated patient is often harrowing. For this reason surgical treatment of cancer patients may be given more liberally than in most diseases. Emphasis must be placed, however, on employing every possible means to insure recovery of the patient with cardiovascular disease who must undergo surgery for the ablation of cancer. This line of procedure has become a cornerstone in the treatment of patients with cancer at Memorial Hospital, and consequently we have been able to collect a rather large series of patients with BBB who have had major surgical operations during a 27 month hospital period.

In this communication the authors have attempted to answer the following questions: (1) Do patients with bundle branch block undergoing surgical procedures have an unusually high imne-

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diate mortality? (2) Does the surgical procedure cause an acceleration or an aggravation of the cardiac disease as manifested clinically or by electrocardiographic tracings? and (3) Do patients with BBB have an unusually high incidence of postoperative complications?

**Method of Study.** Fifty-nine patients with BBB were subjected to major surgical operations at Memorial Hospital from March 1, 1946, to June 1, 1948. During the same period, 13,716 patients were admitted and

incidence. The charts were reviewed and insofar as possible an effort was made to classify the heart disease according to the New York Association Classification. The cardiovascular background was evaluated by noting a history of, or findings of, rheumatic fever, syphilis, hypertension, myocardial infarction, cardiac enlargement or congestive failure. Preoperative management, including the use of digitalis and quinidine; the type, length and course of operative procedure, the anesthesia employed and the postoperative course and care were reviewed. The incidence and variety of postoperative complications were noted with special emphasis

TABLE 1.—ESSENTIAL DATA ACCORDING TO TYPES OF BUNDLE BRANCH BLOCK

		Total Number of Cases (59)	L B B B (18)	A L B B B (12)	R B B B (1)	S Wave (28)
N. Y. Heart Association Classification*	Class I A and B	51	16	11	1	23
	Class II A and B	8	2	1	0	5
Past History (Cardiac)	Infaret	5	2	2	0	1
	Angina	4	2	0	0	2
Diastolic Blood Pressure above 90 mm.	Congestive Failure	8	1	2	1	4
		29	12	2	0	15
X-ray Evidence of Cardiac Enlargement	No X-ray	6	3	2	0	1
	None	39	8	8	0	23
	Slight	8	5	1	1	1
	Moderate	2	0	1	0	1
Post-operative non-fatal medical complications	Marked	4	2	0	0	2
		10	4	1	1	4
Post-operative deaths		6				
	Surgical	3	3	0	0	0
Patients who have survived 19 months or more	Medical	3	0	0	0	3
		10	0	1	0	9

\* There were no cases in Classes III and IV.

L B B B B—Left bundle branch block.

A L B B B—Atypical left bundle branch block.

R B B B—Right bundle branch block.

S Wave—Atypical right bundle branch block.

4,891 electrocardiograms were made—the incidence of BBB being 1.88% of the electrocardiograms made and 0.66% of the hospital admissions. These figures were not corrected for repeated electrocardiograms or readmissions.

We define a major operation as any procedure lasting 1 hour or longer, whether or not a general anesthetic agent was used. The data were analyzed for age, sex, and race

being placed upon a search for those which might have some etiological relation to the presence of heart disease. Bundle branch block was classified according to accepted criteria.<sup>2</sup> The S wave pattern was considered separately, since there is some evidence that it is associated with a better prognosis.<sup>5,7</sup>

**Preoperative Evaluation.** In Table 1 are summarized the essential data of

the preoperative study, the postoperative complications, deaths and prolonged survivals according to the type of bundle branch block found. There were 30 left bundle branch blocks (LBBB), of which 18 were typical and 12 were atypical. There were 29 right

males; 3 patients were colored, 2 males and 1 female; all others were white. In 1 case there was clinical evidence of rheumatic heart disease; in the others, there being no evidence of rheumatic, luetic or congenital heart disease, the etiology of the BBB was probably ar-

TABLE 2.—TYPES OF ANESTHESIA AND OPERATIONS PERFORMED

Type of Operation	No.	Ether	Spinal	Pentothal	Novocaine
Total Laryngectomy	6			4 (1)	2
Radical Neck Dissection	6			6 (1)	
Abdomino-perineal Resection	6	2	4 (2)		
Uretero-intestinal Transplant	5	4 (1)	1 (1)		
Cystectomy	4	1 (1)	3 (1)		
Sigmoid Resection	3	1	2		
Subtotal Gastrectomy	3	2		1	
Radical Mastectomy	4	2		2	
Lobectomy (right upper lobe)	2	2 (1)			
Exploratory Laparotomy	2	1	1 (1)		
Thyroidectomy (one with radical neck dissection)	2	1		1 (1)	
Transurethral Resection	2	1	1		
Total Gastrectomy	1	1			
Transthoracic Cardicectomy	1	1 (1)			
Splenectomy	1	1			
Hysterectomy	1				1
Cholecystectomy	1	1			
Exploratory Thoracotomy	1	1			
Radical Groin Dissection	1				1
Axillary Dissection	1	1			
Perineal Resection	1	1			
Resection of Maxilla	1			1	
Appendectomy	1		1		
Partial Laryngectomy	1			1	
Partial Cystectomy	1	1			
Simple Mastectomy	1	1			
Cervical Rhizotomy	1	1			
Partial Glossectomy	1	1 (1)			
Transverse Colostomy	1	1			
Excision of Vagina	1	1			
Excision Basal Cell Tumor	1			1	
Excision, Carcinoma of Ear	1			1	
Excision of Buccal Mucosa	1			1	
Excision of Sarcoma of Chin	1			1	
Excision of Parotid Tumor	1			1	
Suprapubic Cystotomy	1		1		
TOTAL	69	30	14	21	4

The figures in parenthesis indicate cases with a fall in diastolic pressure to 50 mm. of mercury or below.

BBBs, of which 1 was typical and 28 were of the S wave type. The average age was 66.6 years with the following distribution: 1 was between 41 and 50 years, 9 were between 51 and 60, 30 between 61 and 70, 18 were 71 to 80 and 1 was between 81 and 90 years of age. There were 41 males and 18 fe-

teriosclerotic. A diastolic pressure of 90 mm. of mercury or above was present in 29 or 49% of the patients. The pulse pressures were distributed as follows: 9 were between 31 and 40; 10 between 41 and 50; 11 between 51 and 60; 6, 61 to 70; 9, 71 to 80; 9, 81 to 90; and 5 between 91 and 100. A preoperative

diastolic pressure below 60 mm. of mercury was not observed. All patients had a preoperative hemoglobin of at least 75% (photoelectric)—the standard being 15.5 gm. for males and 14.4 gm. for females. Six patients had a fasting blood sugar of 120 mg. per 100 cc. or more. The blood urea nitrogen was within normal limits in all patients prior to the operation. One patient had clinical evidence of polycythemia. Preoperative medications included the continuance of maintenance

for 1 hour—in all others it was rapidly (within 5 to 20 minutes) restored to normal by neosynephrine subcutaneously or by whole blood transfusions. Six of the 12 cases developing significant hypotension received ether, 3, spinal, and 3, pentothal anesthesia. There were 69 major operative procedures performed on these 59 patients. Seventeen of the operations lasted between 1 and 2 hours, 18 between 2 and 3 hours, 23 lasted 3 to 4 hours, and 11 lasted 4 to 5 hours. In no instance

TABLE 3.—NON-FATAL MEDICAL AND SURGICAL POSTOPERATIVE COMPLICATIONS

Medical	No. of Cases	Surgical	No. of Cases
Bronchopneumonia	3	Urinary Incontinence	2
Atelectasis	2	Wound Abscess	2
Paralytic Ileus	2	Wound Slough	2
Thrombophlebitis	1	Pneumothorax	2
Pulmonary Embolus	1	Wound Dehiscence	1
Tachycardia (P type)	1	Intestinal Obstruction (due to adhesions)	1
		Acute Urinary Retention	1
		Esophageal Fistula	1
		Chyle Fistula	1
		Hematoma	1
TOTAL	10	TOTAL	14

doses of digitalis in the 6 patients who were receiving it when they came to the hospital; and, in addition, 4 patients were given therapeutic doses of digitalis and quinidine preoperatively as a prophylactic measure. There was roentgenological evidence of slight, moderate or marked cardiac enlargement in 14 of the 53 cases in which 6 foot chest films were available. The criteria used were: (1) for slight enlargement, the transverse diameter of the heart exceeded one-half the internal diameter of the chest by 1 to 2 cm. (2) for moderate enlargement, by 3 to 4 cm. and (3) for marked enlargement by 5 or more cm.

*Operative and Postoperative Course.* In Table 2 the operations and anesthetic agents are listed. In 13 cases there was a drop in diastolic pressure to 50 mm. of mercury or below. The pressure remained at dangerous levels in 2 cases

was an operation terminated because of a serious complication arising on the operating table.

As for the postoperative period, there were 6 patients who died from 3 to 19 days after the operation; these will be discussed in more detail below. Parenteral fluids were administered to 8 of the 59 patients as hypodermoclyses—an unusually high incidence since fluids are almost never given subcutaneously in this hospital. There were 10 patients who received 1500 cc. a day of normal saline intravenously for 1 to 4 days and only 1 developed signs of congestive failure. He died on the 16th postoperative day in pulmonary edema after having received large amounts of blood, plasma, saline and 50% glucose by vein; he was found at post-mortem examination to have a recent occlusion of the right coronary artery. Only 2 patients manifested evident cyanosis

during the postoperative period and they, as well as 8 others, received oxygen either by tent or nasal tube. There were 4 patients whose hemoglobin dropped to below 65% after the operation—the lowest being 48%. A transient azotemia with elevation of the blood urea nitrogen from 20 to 44 mg. per 100 cc. was noted in 9 cases. In addition, all but one of the 6 patients who died had significant azotemia. The patients with diabetes were kept under good control and the patient with polycythemia did not

follows: 285, 400, 410, 420, 430, and 530 gm. In 3 cases the cause of death, generalized peritonitis and massive hemorrhage, was regarded as surgical; in the other 3 the causes of death were: coronary thrombosis, pulmonary embolus, and bronchopneumonia with acute pyelonephritis.

**Results.** In Table 4 the follow-up studies on 59 patients with BBB who underwent major operations are presented. There was an immediate postoperative (within 19 days) mortality of 10%; one-half of these were

TABLE 4.—END RESULTS AT DIFFERENT POSTOPERATIVE PERIODS

	3-19 days	Postoperative 3 weeks— 3 months	4-6 months	7-12 months	13-18 months	19-28 months
Immediate postoperative deaths	6					
Surgical	3					
Medical	3					
Deaths from Carcinoma			2	1	3	2
Death, cause not determined			1			
Deaths from heart disease and patients who had increasing cardiac symptoms		1 (tachycardia)	1 (digitalized)	1 (died ? coronary) 1 (digitalized)		
Surviving patients without symptoms due to heart disease		9	5	11	6	8

suffer any unusual complications. In Table 3 the non-fatal medical and surgical postoperative complications have been listed. The average hospital stay was 19.8 days. No correlation was noted between the type or severity of the complications and the form of BBB or the preoperative evaluation.

**Autopsy Findings.** Post-mortem examinations were performed on 7 of these patients, 6 of them having died within 19 days of the operation and 1 died 3 months later. Evidence of myocardial infarction was found in 2 cases; 1 with LBBB and the other with the S wave pattern. The other hearts showed atherosclerosis of the coronary vessels with resultant myocardial fibrosis. The weights of all but one of the hearts were obtained, as

classified as medical deaths. Eight patients have since succumbed to recurrent or metastatic malignant disease which makes it impossible to evaluate what the longevity of these patients would be if the BBB alone were considered. In only 5 cases was there evidence of progression of the heart disease following the operation. One died at home, ostensibly of a coronary thrombosis 8 months after the operation, 2 patients were digitalized after 5 and 8 months, 1 developed angina after 4 months and 1 an unexplained tachycardia after 3 weeks. Ten patients survived 19 to 28 months without any symptoms of heart disease. All but one of these had the S wave type of BBB.



Postoperative electrocardiograms were available in 21 cases and showed insignificant changes in 7 instances as follows: (1) reduction in rate from 71 to 50; (2) change of the QRS conduction time from 0.12 sec. to 0.11 sec.; (3) reduction in amplitude of the T waves 18 months after the operation and 6 months before death from pulmonary metastases; (4) inversion of TCF<sub>4</sub>; (5) the development of a high TCF<sub>4</sub>; (6) the appearance of periods of 2-1 auriculo-ventricular block, and (7) the appearance of numerous auricular and ventricular premature beats (2 cases).

sure, the cardiac size, the non-fatal medical complications, the postoperative deaths and the number of patients who survived 19 months or more after their operations. Study of this table fails to show any significant correlation between the type of BBB and the presence or absence of any of the factors just listed. In other words, there was no significant difference relatable to the type of BBB in the distribution of the number of patients with cardio-vascular symptoms; the number of patients with a history of angina, infarction or congestive failure; the presence of hypertension or cardiac

TABLE 5.—ELECTROCARDIOGRAPHIC DATA ACCORDING TO THE TYPE OF BUNDLE BRANCH BLOCK OBSERVED

	L B B B No. of patients 18	A L B B B No. of patients 12	R B B B No. of patients 1	S Wave No. of patients 28
P-R interval (sec.)				
.12-.20	16	12	1	23
.21-.23	0	0	0	2
.24-.26	1	0	0	0
Not determinable*	1			3
	(idio- ventricular)			(Auricular fibrillation)
QRS interval (sec.)				
.12-.13	13	11	1	22
.14-.15	5	1	0	6
Q-T interval (sec.)				
.31-.40	12	10	1	21
.41-.43	2	0	0	4
.44-.48	3	2	0	3
.49-.50	1	0	0	0
Avis				
Normal	4	2	0	7
Left	14	10	0	15
Right	0	0	1	6

\* 3 had auricular fibrillation; 1 had idio-ventricular rhythm.

Four patients with the S wave or R B B B finding had significant Q waves in the limb or precordial leads.

**Electrocardiographic Findings.** To recapitulate, 59 patients with bundle branch block were studied; of these 18 had typical left bundle branch block; 12, atypical left bundle branch block; 1 typical right bundle branch block; and 28 atypical, or S wave, right bundle branch block. In Table 1 the type of BBB is presented with respect to the classification of the type of heart disease and the cardiac past history. the diastolic blood pres-

enlargement; the incidence of medical complications; or the number of deaths due to medical complications. We are forced to conclude that the type of BBB in this series bore no relation to the extent of heart disease preoperatively or to the operative or postoperative course. A later follow-up may give interesting data on the survival rate, without recurrence of cancer, in the various groupings. The period of postoperative observation is not yet

long enough to permit conclusions as to the significance of the 19 to 28 months survival of 9 patients with S wave BBB as against only 1 survival of another type of BBB (atypical left).

No conclusions can be drawn from the mortality in this series, since there were but 6 deaths; we can merely state that the 3 patients succumbing to strictly surgical complications had left BBB and that the 3 dying from medical complications had right BBB of the S wave type. Five patients developed increasing cardiac symptoms postoperatively, 2 had LBBB, none had RBBB, 2 had S wave RBBB, and 1 atypical LBBB.

Table 5 gives the PR, QRS and QT times, the axis deviation and the various types of arrhythmia observed in the 4 types of BBB. The distribution of prolonged PR, QT, and QRS times is not significant according to the type of BBB; but of the whole group, 3 patients had PR intervals that were above normal; in 12 patients the QRS deviation was greater than 0.13 sec.; and in 15 the QT interval was above normal for the heart rate. Left axis deviation was seen in 24 patients with LBBB and in 15 with the S wave type of RBBB.

**Discussion.** Although it was not possible to get a comparable series of patients of the same average age (66.6 years) as the patients studied, we were able to obtain the operative mortality statistics on patients 60 to 71 years of age who underwent sub-total gastric resections, abdominal perineal resections and radical neck dissections for carcinoma at Memorial Hospital. The operative mortality for 32 patients who had sub-total gastric resections in this age group was 12.5%; for 64 patients who had abdominal perineal resections it was 3.3%; and for 164 patients who underwent radical neck dissection 2.3%, giving an average of 3.4% for the 260 patients.

The immediate postoperative mor-

ality of the series of 59 patients with bundle branch block was 10% (6 deaths). However, 3 deaths were unrelated to the presence of heart disease, generalized peritonitis being responsible in 2 instances and uncontrollable hemorrhage in 1. One patient died from acute pyelonephritis following ureteral transplants to the bowel but was shown to have bronchopneumonia as a contributory cause of death at autopsy. If this patient is included as a medical death related to the presence of heart disease, the "medical" postoperative mortality is 5%; if this death is excluded it is 3.3%, indicating that the presence of bundle branch alone was of questionable importance in evaluating the operative risk in these 59 patients.

Only 3 patients developed symptoms and signs of congestive heart failure postoperatively, easily controlled in 2 instances and associated with fatal infarction in 1 patient. The incidence of medical and surgical postoperative complications was not excessive. Finally, it was observed that increasing cardiac symptoms occurred in 5 patients several weeks to months following discharge from the hospital.

Although the data demonstrate that the presence of bundle branch block does not by itself constitute a contraindication to major surgical procedures today, there is an increased risk in such patients which can be kept at a minimum by meticulous medical management. Preoperative care, the choice of anesthesia, and careful postoperative management have made it possible to treat surgical problems in such patients. The careful supervision of fluid and salt intake, the judicious use of digitalis, diuretics and oxygen and the wide availability of potent antibiotics facilitate the medical management of such patients; close cooperation between the surgeon and the internist is of the utmost importance.

Emphasis must be placed upon an adequate evaluation of the medical history, cardiac classification and physical findings rather than upon electrocardiographic evidence of bundle branch block. This electrocardiographic abnormality, in the absence of contraindications uncovered by careful medical consultation, should not influence either the surgeon or the internist in deciding upon the surgical management of the patient with cancer. Both may have reasonable expectations that the patient will survive the operation and that his heart disease will not be accentuated as a result of surgery.

The cardiac status of a patient is neither more nor less important than evaluation of the pulmonary, renal, neurological, metabolic or hormonal functions and over-emphasis of any one aspect of a medical or surgical problem may lead to disaster. It is of interest that of all patients with bundle branch block seen during the period of time covered by this study, only 3 were thought to be too poor as operative risks to withstand even palliative surgery.

The fact that none of our patients could be classified as having heart disease more severe than Class II B undoubtedly accounts, in part, for the relatively low operative mortality among the 59 patients studied. A greater mortality would be expected among patients with bundle branch block whose heart disease was classified as Class III or IV.

#### Clinical Summaries of the 6 Cases Who Died Within 19 Days of the Operation.

CASE 1. J. R., a 76 year old white male, entered the hospital on 12/20/46, complaining of painless hematuria of 1 year's duration. Four years ago he had had an episode of acute left-sided heart failure thought to be due to a myocardial infarction. Physical examination revealed a fairly well-developed elderly male who weighed 142 lbs. and had a blood pressure of 160/120. The heart appeared to be slightly enlarged to the left. There was normal sinus rhythm and no evi-

dence of heart failure. The electrocardiogram showed an S wave type of RBBB. The heart was found to be at the upper limits of normal size on Roentgen-ray examination. A suprapubic cystotomy was performed, lasting 1 hour under spinal anesthesia. The blood pressure dropped to 110/70 but responded rapidly to the subcutaneous injection of 3 minims of 1:1000 neo-synephrine. Postoperatively the hemoglobin was 78% of normal and the blood urea nitrogen rose from 18 to 23 mg. per 100 cc. The urinary output was poor. The patient became irrational, was put in an oxygen tent and given several hypodermoclyses containing saline. He died on the 16th post-operative day (1/14/47) in pulmonary edema.

At post-mortem examination the heart was found to weigh 530 gm. There was complete obliteration of the right coronary artery and a large old infarct with aneurysm formation involving the left ventricle.

CASE 2. A. T., a 75 year old white female entered the hospital on 6/30/47, complaining of epigastric distress of 1 year's duration. She had been slightly dyspneic for 1 year and thought that she was hypertensive. She was found to be well-nourished, weighed 159 lbs., and her blood pressure was 170/90. The heart appeared to be slightly enlarged to the left and there was a grade II, blowing systolic murmur at the apex. The lungs were clear and there was no ankle edema. The heart appeared slightly enlarged to the left on Roentgen-ray examination. The electrocardiogram showed an LBBB. The hemoglobin was 100% of normal. She received digitalis and quinidine before the operation as a prophylactic measure. A total gastrectomy was performed with ether and curare anesthesia. The operation lasted 3½ hours. The blood pressure fell briefly to 110/70. After the operation the temperature rose to 104° and 105° in spite of antibiotics. The patient died on the 14th post-operative day (7/27/47).

At post-mortem examination the heart was found to weigh 430 gm. The coronary arteries were patent. There was no evidence of cardiac failure. A leaking suture line had resulted in generalized peritonitis.

CASE 3. F. G., a 64 year old white male entered the hospital on 5/31/46 complaining of epigastric distress, anorexia and a 45 lb. weight loss during the previous 6 months. He was found to be fairly well-nourished and to weigh 178 lbs. The blood pressure was 110/70, the anteroposterior diameter of the chest was increased, and the breath sounds were distant. The electrocardiogram showed the S wave type of right bundle branch block. Roentgen-ray examination showed the heart was not enlarged. The preoperative hemoglobin was 100% of normal. A transthoracic

cardiectomy which lasted 5 hours was performed using ether anesthesia. The blood pressure fell to 96/60 for 10 minutes during the operation. An electrocardiogram taken after the operation showed inversion of T<sub>3</sub> and depression of QRS in the precordial leads. Except for an occasional rise in temperature to 101° the patient appeared to be doing well. He died suddenly on the 10th postoperative day (6/20/46).

At post-mortem examination a pulmonary infarct of the left upper lobe was found. The heart weighed 420 gm. There was no evidence of myocardial infarction.

CASE 4. L. E., a 74 year old white male entered the hospital for the first time on 2/3/47 complaining of intermittent hematuria of 6 months' duration. The past history was non-contributory. The patient was found to be a poorly nourished elderly male with a blood pressure of 130/80. There were a few coarse rhonchi throughout both lung fields. The heart was not enlarged to percussion and there was no ankle edema. The preoperative hemoglobin was 99% of normal. An electrocardiogram showed the S wave type of RBBB. Roentgen-ray examination showed the heart was not enlarged. The patient underwent an uneventful transurethral prostatectomy under spinal anesthesia. One month later he returned to the hospital in the same general condition and a bilateral uretero-intestinal transplant was performed. The operation lasted 3 hours. The blood pressure was 60/20 for 1 hour, and the patient received a total of 11 minims of 1:1000 neosynephrine subcutaneously. During the postoperative period the patient's pulse ranged from 130 to 140 and the temperature rose to 102. He received 8 cc. (1.6 mg.) of Cedilanid on the 2nd postoperative day. He died on the 3rd postoperative day (3/8/47).

At post-mortem examination acute pyelonephritis and bronchopneumonia were found. The heart weighed 410 gm. There was moderate atherosclerosis of the coronary vessels.

CASE 5. M. B., a 70 year old white female entered the hospital on 12/10/46 complaining of constipation and generalized abdominal cramps of 4 months' duration. The past history was non-contributory. She was well-nourished and the blood pressure was 150/96. The heart and lungs were normal. An electrocardiogram showed an LBBB. Roentgen-ray examination showed the heart was not enlarged. The hemoglobin was 95% and fasting blood sugars were 100 and 109 mg. per 100 cc. before the operation. An exploratory laparotomy and transverse colostomy were performed with spinal anesthesia. The operation lasted 1½ hours. The blood pressure dropped from 120/80 to 80/60 for 10 minutes and she twice received 3 minims of 1:1000

neo-synephrine subcutaneously. Following the operation the patient received insulin according to the pre-meal urine specimen as well as intravenously with infusions of dextrose and water. On 2 occasions she complained of weakness and sweating. Shortly after one of these episodes the blood sugar was found to be 74 mg. per 100 cc. She also complained of precardial pain radiating down the left arm. An electrocardiogram showed no significant change from the preoperative tracing. The patient received 1.2 mg. of digitoxin intravenously on the 2nd postoperative day. She died 12/19/46.

At post-mortem examination fecal contamination of the peritoneum due to leakage around the stoma was found. There was atelectasis of both lower lobes. The heart was said to be slightly hypertrophied but its weight was not recorded. There was moderate sclerosis of the coronary vessels but no thrombosis was observed.

CASE 6. H. H., a 59 year old white machinist entered the hospital on 2/20/48 complaining of pyuria of 6 months' duration. The past history was non-contributory. Physical examination revealed a well-developed, well-nourished male who weighed 171 lbs. The blood pressure was 160/70. The heart and lungs were normal; there were no signs of congestive heart failure. The preoperative hemoglobin was 92% of normal. The electrocardiogram showed an LBBB; and the heart was observed to be slightly enlarged on Roentgen-ray examination. Eleven days after admission a left uretero-intestinal transplantation was performed with ether anesthesia. The operation lasted 2½ hours and was uneventful. Two days after the operation the temperature rose to 101 and signs of atelectasis were noted. The signs subsided rapidly, and 15 days after the operation the patient was returned to the operating room where a cystectomy, right nephrectomy and prostatectomy, were performed with ether anesthesia. The procedure lasted 5 hours, the patient received 2500 cc. of whole blood and the blood pressure did not fall below 100/60. Immediately following the operation the patient was noted to be cold and sweaty and the blood pressure dropped to 110/70 from 130/90. An electrocardiogram showed no change and a blood transfusion gave prompt relief. The day after the operation signs of atelectasis were noted which responded to intratracheal aspirations. He was also digitalized as a prophylactic measure at this time. On the 8th postoperative day bilateral calf tenderness and pain in the left chest developed, whereupon intravenous heparin was administered for 5 days with good response. Six days after the last dose of heparin the patient began to bleed profusely from

the suprapubic wound; and, in spite of careful packing and blood transfusions he died on the following day (4/6/48), 19 days after the 2nd operation.

At post-mortem examination the heart was found to weigh 400 gm. There was no evidence of edema, consolidation or infarction in the lungs. There was a fistulous communication between the ileum and the pelvic cavity. The cause of death was a massive hemorrhage at the operative site in the suprapubic area, the exact source of which could not be determined.

**Summary and Conclusion.** 1. Fifty-nine patients (average age 66.6 years) with bundle branch block were subjected to major surgical operations. Two patients died 10 and 16 days post-operatively of medical complications, a 3.3% operative mortality to which the presence of heart disease presumably contributed. The total operative mortality, including strictly surgical complications, was 10%.

2. The operative mortality in 280 patients 60 to 71 years of age subjected to total gastrectomy (32 patients),

abdominal perineal resection (64 patients) and radical neck dissection (164 patients) was 12.5%, 3.3% and 2.3% respectively, an average mortality for the 3 operations of 3.4%.

3. The presence of bundle branch block *per se* does not constitute a contraindication to surgical intervention. Careful classification of the heart disease and study of the functioning of other systems are of greater importance in evaluating operative risk.

4. Postoperative complications did not appear to be more frequent or more severe than might be expected for a comparable group of patients in the same age group.

5. No significant correlations could be demonstrated between the electrocardiographic and the clinical findings. The stress on the circulation imposed by the surgical procedure apparently did not aggravate the course of the heart disease.

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# THE EFFECT OF ROENTGEN RADIATION ON THE PRODUCTION OF THORACIC DUCT LYMPHOCYTES\*

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IT HAS been widely recognized that lymphoid tissue is among the most sensitive indicators of damage by Roentgen radiation. Further, after large doses of radiation the blood lymphocytes disappear very rapidly from the peripheral blood and are virtually completely absent in 24 hours or somewhat less after the radiation is administered. It is the purpose of this report to record the changes in the numbers of thoracic duct lymphocytes and rate of flow of thoracic duct lymph in cats receiving a large, single dose of whole body Roentgen radiation.

**Procedures.** Thoracic duct cannulations were performed in 9 normal animals receiving no Roentgen irradiation and in 11 animals who were to receive 1500 r whole body irradiation. Lymph was collected in hourly or 2-hourly volumes in a graduated centrifuge tube and was prevented from clotting by the addition of 3 drops of 1% sodium heparin to the collecting container. After mixing, the lymphocyte count per c. mm. was determined in duplicate, the specimen volume recorded, and the total lymphocytes in the specimen computed. In each instance the values for the first 2 hours were designated as a baseline and expressed as 100%. The values for each succeeding specimen were then expressed as a ratio or percentage of the baseline. The first group of animals received no irradiation; the second group were irradiated after baseline values were determined.

The whole body irradiation in the amount of 1500 r uniformly results in the death of cats within 4 to 7 days. It is far in excess of the amount required to accomplish virtually

complete disappearance of lymphocytes from the peripheral blood in 24 hours or less. The following factors were kept constant: Total dosage, 1500 r; K.V.P., 250; Milliamperage, 15; Target distance to center of cat, 22"; Filter, Aluminum parabolic +  $\frac{1}{2}$  mm. of copper; Half value layer, 2.15 mm. copper; Average rate of administration, 25 r per minute.

**Presentation of data.** It is not valid under the experimental procedure employed to estimate the changes in thoracic duct lymphocytes and in lymph flow purely on the basis of a comparison of values obtained before and after irradiation. It has been the experience of this laboratory that as a result of the procedure itself there is over a period of several hours some diminution in the rate of lymph flow, the total lymphocytes per unit of time, and, to a much lesser extent, of the numbers of lymphocytes per c. mm. of lymph. This occurs whether the animal is irradiated or not. It is therefore necessary to compare irradiated animals with non-irradiated animals that have been submitted to the same experimental procedure if valid conclusions are to be drawn.

The data are presented graphically in Figure 1. In the control group data are available for only 6 hours after the baseline.

**Analysis and discussion of data.** It can be seen that following 1500 r whole body irradiation, the lymphocyte count per c. mm. and the total lymph

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phocytes per unit of time in thoracic duct lymph of cats rapidly become depressed when comparison is made with determinations in normal animals subjected to cannulation. This is apparent within 2 hours after the beginning of irradiation and has become very marked after 6 hours. The changes in lymph volume suggest some reduction in lymph flow in the irradiated group, but with the relatively small number of animals on which data are

tuallly, some 12 hours after irradiation was begun, the counts fell to low values. It is well to include such exceptions to the general pattern of behavior after irradiation in order to illustrate the marked individual variation in the response of experimental subjects to radiation injury. However, in 6 animals the total lymphocytes were less than 15% of baseline values 6 hours after irradiation, while 8 hours after radiation was given this factor had fallen

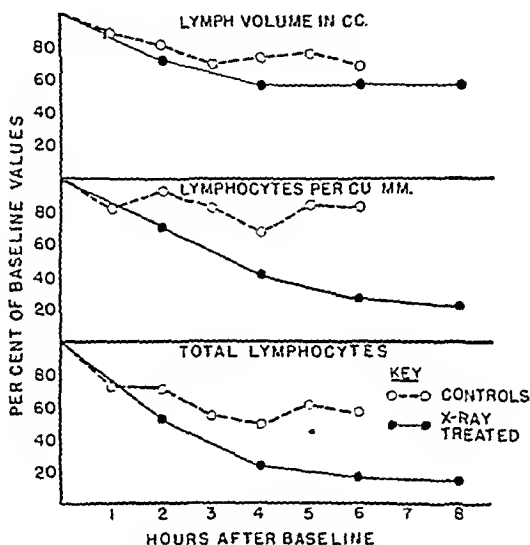


Fig. 1.—The mean values of normal and irradiated groups of cats are compared as regards lymph volume, lymphocytes per c.mm., and total lymphocytes per unit of time. In every instance the values for each specimen were expressed in each animal as a percentage of the baseline determination in the same animal, and then these percentages averaged for the group. In the irradiated group 1500 r whole body irradiation was begun at "O" hour and completed in about 1 hour. The studies were made on thoracic duct lymph.

available this may not be significant. The figures given are mean values, and, in the case of the irradiated group, are weighted somewhat high by the inclusion of a single animal whose behavior differed inexplicably from the remainder of the group. In this animal the total lymphocytes and lymphocytes per cu. mm. did not progressively fall in number but after a preliminary reduction actually remained relatively stationary for several hours after irradiation. This animal was followed for a considerable period of time, and even-

to less than 10% of baseline in 6 animals. In 3 animals the lymphocyte count per c. mm. of lymph was less than 6% of the baseline 8 hours after irradiation.

There is rather strong reason to believe that mature leukocytes are detectably damaged only by tremendous doses of Roentgen radiation (much larger than those given here), and that it is the precursor cells which are so very sensitive to penetrating radiations. It is, of course, not possible to say that mature cells subjected to radi-

ation may not be destroyed at a rate more rapid than normal despite the apparent lack of morphologic damage. It does seem likely, however, that fully matured lymphocytes present in the lymphoid tissue at the time of irradiation can be expected later to appear undamaged in considerable numbers in the lymph draining those tissues. If such is the case the lymphocytes found in the thoracic duct lymph following 1500 r whole body irradiations are: (1) the progeny of cells still capable of undergoing mitosis for one or more times after irradiation (2) lymphocytes which were relatively mature at the time of irradiation and which were subsequently washed out morphologically intact by the flow of lymph through the nodes. In short, the joint phenomena of production plus release from storage account for the continued presence of lymphocytes in thoracic duct lymph for a time after heavy irradiation.

It is a fact that in these experiments the irradiated group of cats were able to produce in the first 8 hours after irradiation a total of only 104% of the number of lymphocytes produced in the 2 hours before irradiation. At the end of this 8-hour period the numbers of lymphocytes present were so small as to be almost negligible and were continuing to be reduced further. In addition, if the first 2 hours after the start of irradiation are disregarded, the animals were able to release in the subsequent 6 hours only 51.7% of the numbers of lymphocytes released during the 2-hour pre-irradiation period. Not all of this reduction in lymphocyte numbers can be attributed to the effects of irradiation. Part of it is artifact in that it results from the experimental technique since normal, untreated animals in control groups produced only 7/12 as many lymphocytes during a 6-hour period as would be anticipated from the baseline determinations. Using the reciprocal of this

value, 12/7, we can correct to a reasonable degree the values obtained in the irradiated group.

When this is done we find a "corrected" value of 178% of the number of lymphocytes produced in a 2-hour pre-irradiation period released in the 8 hours after irradiation. Again neglecting the first 2 hours after the start of irradiation, the "corrected" figure for the subsequent 6 hours is 88.6% of the total lymphocytes produced in the baseline period. At the end of this time lymphocyte release was nearly at a standstill. Stated otherwise, if lymphocyte release subsequent to the 8th hour after irradiation is disregarded as negligible, the sum total of combined production plus release of mature cells from the lymphocyte warehouses after 1500 r whole body irradiation is begun amounts to somewhat less than a normal 4-hour supply. Moreover, within 2 hours after the start of irradiation, a potential of a little less than 2 hours' normal supply of lymphocytes remains in the nodes drained by the thoracic duct. If mature lymphocytes are not damaged severely by Roentgen radiation of this degree, then a reserve stock of less than 4 hours' normal supply is present within the lymph nodes; if all the lymphocytes released resulted from continuing production (as is highly unlikely), then no more than a 3 to 4 hour supply could be produced from the time irradiation was begun. If the former conditions are assumed the mature lymphocyte reserve is small indeed, while in any event production must cease or nearly cease quite promptly after severe radiation injury.

The above release of lymphocytes into the thoracic duct after 1500 r whole body irradiation can be employed to compute capacity for replenishment of the peripheral blood. If we assume our average cat to weigh 3 kg. the average blood volume (on a 5% of body weight basis) to be 150 cc.,



the average leukocyte count to be 15,000 per c.mm., and 25% of the cells to be lymphocytes, one can readily compute the average absolute lymphocytes to be  $562.5 \times 10^6$ . The number of the total number of circulating lymphocytes to be  $562.5 \times 10^6$ . The number of lymphocytes released in the 8 hours subsequent to the start of irradiation, even when "corrected" for the experimental procedure, could not exceed  $314.8 \times 10^6$ . Therefore, if the small number released after the 8th hour is disregarded, enough lymphocytes sufficient to replace slightly more than one-half the circulating lymphocytes are found in thoracic duct lymph after the amount of irradiation employed in these experiments. The computations

admittedly lack strict quantitative accuracy, but it should be possible to rely on the order of magnitude of the changes observed.

**Conclusions.** The sum reserve of lymphocytes in the lymphoid tissues drained by the thoracic duct in cats is very small. From the time 1500 r whole body irradiation is *begun*, the total number of lymphocytes subsequently appearing in thoracic duct lymph amounts to no more than approximately a normal 4 hours' supply. Following this amount of Roentgen irradiation the numbers of lymphocytes in thoracic duct lymph very rapidly decrease, the reduction being noted within a very short time after irradiation is begun.

# CONGENITAL HEMOLYTIC JAUNDICE IN A NEGRO FAMILY

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CONGENITAL hemolytic jaundice is considered to be extremely rare in the Negro race. Wintrobe<sup>7</sup> encountered only one instance in a Negress of mixed blood. Scherer and Cecil<sup>5</sup> reported another case in a 14 year old Negress, and stated that in their rather extensive experience with Negro blood, this was the first case they ever noted. They also quoted Kracke and Haden as never having encountered any. Strag-nell and Smith<sup>6</sup> observed three examples of this disease among 5 Negro siblings. In reviewing the records of the Presbyterian Hospital (New York), where Negroes constitute approximately 10% of the patients, these authors found 78 examples of congenital hemolytic jaundice in white, but only 1 in a mulatto woman. Goodman and Cates<sup>2</sup> studied another Negro family which included 3 sisters suffering from congenital jaundice. The only other possible instance in the literature is that of Merskey and Baskind<sup>4</sup> in an African native. This case had all the features of congenital jaundice, but because the family could not be studied, the authors were not able to rule out the possibility of its being acquired.

In the present report we wish to add three more cases of congenital hemolytic jaundice in a Negro mother and 2 daughters.

Case Reports. CASE 1. M. R. W., mother, age 38, was first observed in another hospital where, in November, 1944, she was treated for pneumonia and latent syphilis (Wassermann 4+, Kline 4+). At that time she was discovered to have anemia with hemoglobin

of 58% and red cell count of 2.28 million, but no special studies were made to determine the type of anemia.

She was readmitted to the same hospital 6 months later (May, 1945) by ambulance, in a semi-comatose condition. Previous to this admission she had complained of increasing weakness, abdominal pains and inability to do her housework. These symptoms became progressively worse until she lapsed into stupor. On admission, the blood pressure was 110/70, pulse imperceptible. The eyeballs were yellow and the mucous membranes very pale. There was evidence of pneumonia posteriorly on the right. Roentgenograph of the chest showed also enlargement of the heart, mainly to the right. The liver was palpable and tender. No mention was made of the size of the spleen.

Laboratory examination showed 1+ albumin and some red cells in the urine. Admission hemoglobin was 15%, red cell count 830,000 with 3.9% reticulocytes. Platelet, white cell count and differential were within normal limits. The red cells exhibited slightly increased fragility to hypotonic solution of saline, with hemolysis beginning at 0.47% and completed at 0.34%. Icterus index was 10. Sternal aspiration showed normal marrow with myeloid-erythroid ratio of 4 to 1. Wassermann reaction was 2+, Kline 4+.

The patient was treated with blood transfusions, the first 2 of which were accompanied by reactions. She was discharged approximately 1 month later with hemoglobin of 48%.

She was admitted to the Barnert Memorial Hospital nearly 3 years later, on April 19, 1948. In the interim she had been reasonably well, and bore one child, her seventh, without complications. Nine days previous to the present admission, the patient delivered a female infant, her eighth child, at home, spontaneously and without any immediate difficulties. However, on her third postpartum day, she developed generalized abdominal pain with vomiting and fever. After a few days the pain localized in the right upper

quadrant and right costovertebral area. The urine became darker in color and sclerae turned slightly yellow.

On examination the patient had typical Negroid features and dark brown skin. Temperature was 99.4°. The skull was "tower-shaped" (Fig. 1A), the sclerae slightly jaundiced, the mucous membranes very pale. There was a blowing systolic murmur at the apex. Roentgen-ray of the chest revealed moderate enlargement of the heart, mostly to the right. The liver extended approximately 2 fingerbreadths below the right costal margin and the firm tip of the spleen could be definitely felt on inspiration. The uterus was well involuted. There was no evidence of recent or old ulcerations of the legs.

the fear of reactions. The patient improved gradually, her temperature remained normal, and she was discharged with a hemoglobin of 7 gm. Splenectomy was refused.

As of last examination (June, 1948), she was asymptomatic except for slight yellow tint of the sclerae. The spleen was not palpable and hemoglobin was 9 gm.

CASE 2. A. R., age 9, daughter of M. R. W. (Case 1). This child was admitted to another hospital at the age of 6 years in May, 1945. Her illness coincided with that of her mother (see above) and manifested itself with similar symptoms, mainly, progressive weakness, epigastric distress and jaundice of one week's duration. Except for usual childhood diseases, she was apparently well until the onset

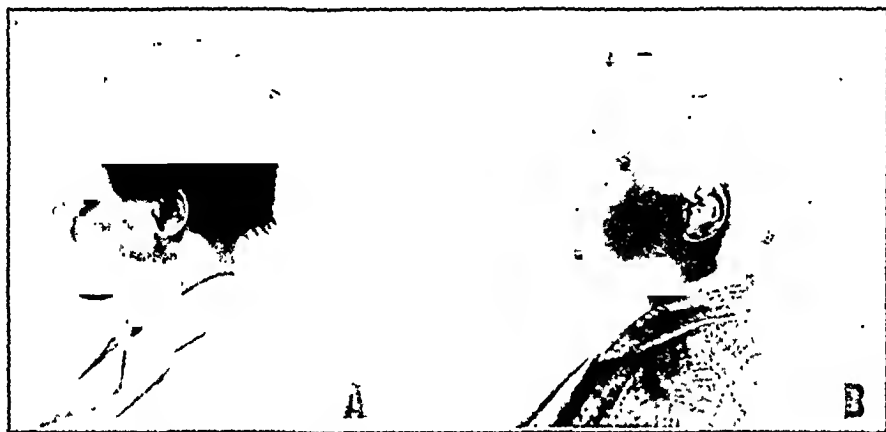


FIG. 1.—A—Case 1. B—Case 2. Tower-shaped skull, more marked in A.

Laboratory examination showed severe anemia with marked spherocytosis and reticulocytosis, increased fragility of red cells and markedly increased excretion of urobilinogen in the urine (Table 1). The latter gradually decreased from 1:1200 to 1:40 (method of Wallace and Diamond), but even before discharge, 10 days later, she still excreted 380 mg. of urobilinogen in 24-hour stool specimen. Test for hemolysins in serum was negative. There was some evidence of temporary liver disturbance; cholesterol ester was reduced to 50% of total, and the albumin:globulin ratio was reversed, 2.3/3.5; cephalin-cholesterol flocculation test showed a 3+ reaction shortly after admission, but became negative on the day of discharge. Serological tests for syphilis gave the following results: Mazzini 4+, Kahn 1+, Kolmer  $\pm$ . Roentgen-ray of the skull showed considerable thickening of the calvarium with widening of the diploic space, and some distortion in the outline of the clinoid processes of the sella turcica (Fig. 2A).

Therapy consisted solely of high protein diet. Transfusions were withheld because of

of the present illness. Her temperature at the time of admission was 104°. The mucous membranes were very pale and the conjunctivae jaundiced. On Roentgen-ray examination, there was moderate enlargement of the heart, mostly to the right. The liver was 2 fingers and the spleen 1 finger below the costal margins.

Laboratory studies showed a hemoglobin of 22%, red cell count less than 2 million, reticulocytes 5%, increased fragility of red cells (beginning hemolysis of 0.50% saline, complete in 0.38%), icterus index of 14, and negative Kline test.

She remained in the hospital for 3 months running a febrile course. The spleen increased in size, then gradually decreased, and the fever abated. Therapy consisted of iron, liver extract and blood transfusions. Splenectomy was suggested but refused. She was discharged with a hemoglobin of 45% and red cell count of 3.0 million.

On examination at the Barnert Memorial Hospital clinic, in June, 1948, the child presented no complaints. She had been comparatively well for the past 3 years. She was

rather small for her age, but otherwise fairly well developed. Her skin was dark brown, the skull "tower-shaped" though less distinctly so than that of her mother's. (Fig. 1B). The sclerae were slightly jaundiced. The spleen could not be palpated. Roentgenograph of the skull revealed marked thickening of the

Table 1). Aside from manifestations of her pulmonary condition, clinical examination was essentially negative. The spleen could not be palpated, though it appeared to be enlarged on Roentgen-ray films. Roentgenogram of the skull revealed no significant changes.

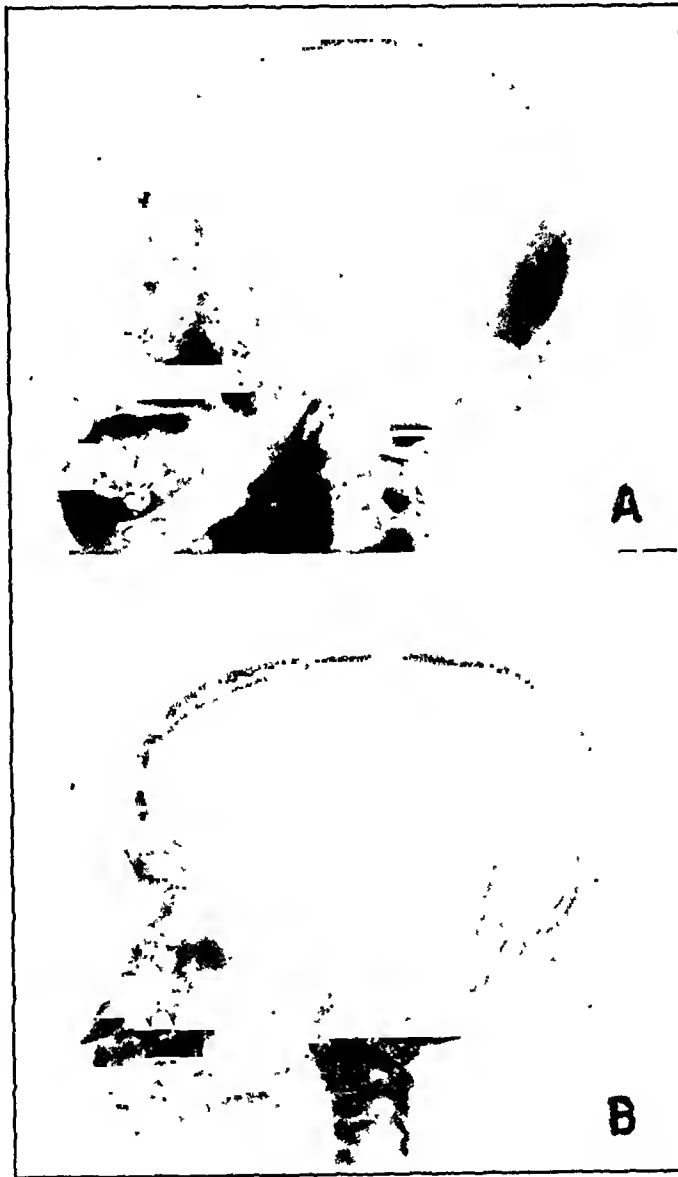


FIG. 2.—A—Case 1. B—Case 2. Thickening of the calvarium and widening of the diploic space.

frontal and parietal bones with widening of the diploic space and partial absorption of the outer table (Fig. 2B). The laboratory data are summarized in Table 1.

CASE 3. Do. R., age 5 daughter of M. R. W. (Case 1). For the past year and a half, this child has been treated in a sanatorium for adult type of pulmonary tuberculosis and was known to be anemic (hemoglobin 45%). Detailed study of the blood revealed changes typical of congenital hemolytic jaundice (see

STUDY OF THE FAMILY. In addition to the 3 members described above, the family consisted of 4 other children by the first husband (who had died of tuberculosis), and 2 more children by a second husband. None of these 6 children had congenital hemolytic jaundice, though all of them were slightly or moderately anemic, probably be-

Table -  
Clinical Hematologic Data in 10 Members of a Negro Family, 3 of whom have Hemolytic Jaundice.

Name	Relationship	Age (Years)	Splenomegaly	Jaundice	Hemoglobin Gm. per 100 cc.	Red Blood Cells Million/cu. mm.	Hematocrit (Per cent)	Mean corpuscular hemoglobin (g)	Mean corpuscular volume (cu. $\mu$ )	Mean corpuscular diameter ( $\mu$ )	Mean corpuscular thickness ( $\mu$ )	Spherocytes (Per cent)	Reticulocytes (Per cent)	Fragility of Red Cells		Sickling	Icterus Index	Urinary urobilinogen	Remarks
														Beginning hemolysis	Complete hemolysis				
M.R.W.	Pl.	37	+	+	6.5	2.6	19	25	72	6.4	2.25	20	14	.64	.40	0	20	Incr.	Congenital hemolytic jaundice Tower skull
D.L.R.	D	11	0	0	10.0	3.9	33	26	85	7.2	2.10	13	0.1	.42	.32	0	6		
A.R.R.	D	9	+	+	8.0	3.3	24	24	73	6.3	2.35		9	.58	.38	0	20	Incr.	Congenital hemolytic jaundice Tower skull
A.L.R.	S	8	0	0	10.0	4.0	33	25	84	7.2	2.08		0.2	.40	.30	0	5		
W.R.	S	7	0	0	9.0	3.4	30	26	88	7.3	2.10		0.3	.40	.30	0	5		
Do.R.	D	5	+	0	8.5	3.2	22	26	70	6.2	2.35	12	9	.60	.38	0	12	Sl. Incr.	Congenital hemolytic jaundice
H.R.	S	4	0	0	10.0	3.6	33	28	91	7.8	1.90		0.2	.38	.24	0	3		
Cn.W.	D	22m	0	0	9.0	4.3	31	21	72	7.1	1.85		0.8	.38	.26	0	5	Normal	
J.W.	D	7w	0	0	9.5	3.9	25	24	64	6.7	1.85		3.8	.44	.34	0	4		
Co.W.	H	40	0	0	14.0	5.0	40	28	80	8.1	1.54		0.3	.36	.22	0	4		

D - Daughter  
S - Son  
H - Husband

Significant data are underlined.

cause of nutritional deficiencies (see Table 1). In the youngest of the children (J.W.), anemia was distinctly microcytic, but there was no spherocytosis and fragility of red cells was within normal limits. One of the boys (A.I.R.) had a suggestion of a "tower-shaped" skull without any Roentgen-ray evidence of increased marrow activity. The second husband (Co.W.) showed approximately normal hemoglobin and red cell count but his mean corpuscular diameter was low and red cell fragility was distinctly decreased. One of his children (Cn.W.), and the youngest child by the first husband (H.R.) also showed decreased fragility. In none of these 3 persons, and for that matter in none of the members of the entire family, was there any evidence of the sickling trait. All members belonged to blood group O, Rh positive, and all, with the exception of the mother, were serologically negative. All were dark brown in color and had distinct Negroid features.

**Comment.** The diagnosis of congenital jaundice in all 3 cases is well established by the typical clinical and laboratory findings and the familial incidence. Skull roentgenograms in Cases 1 and 2 are quite characteristic of a chronic hemolytic process, or better, of marrow hyperplasia associated with this condition. Such changes in the bones are more often seen in Cooley's anemia or sickle cell anemia, but are occasionally found also in congenital hemolytic jaundice.<sup>1</sup>

Hemolytic crises occurred in Cases 1 and 2 on one occasion simultaneous-

ly. These simultaneous crises in several members of a family have been commented upon by some observers.<sup>3</sup>

The rarity of congenital hemolytic jaundice in the Negro race raises the question as to whether the few reported cases are caused by admixture of white blood.<sup>5</sup> Such admixture was obvious in some cases,<sup>7</sup> but not in others. The family presented here as well as the one studied by Stragnell and Smith<sup>6</sup> were typical Negroes as far as facial features and color of the skin are concerned. If true cases of congenital hemolytic jaundice in African natives, similar to the one reported by Merskey and Baskind<sup>4</sup> are found, then the hypothesis of miscegenation will become unnecessary.

**Summary.** 1. Three typical cases of congenital hemolytic jaundice were encountered in a Negro family consisting of 10 persons.

2. In 2 of them, mother, aged 38, and daughter, aged 9, the disease was quite severe, accompanied by hemolytic crises and typical Roentgen-ray changes in the bones of the skull. In the third case, daughter, aged 5, there were typical blood changes, but as yet few clinical manifestations.

3. Review of the literature shows that congenital hemolytic jaundice is very rarely found in the Negro race.

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We are indebted to the staff of the Paterson General Hospital for data of previous admission in Cases 1 and 2, and to the staff of the Valley View Country Sanatorium for some of the clinical and roentgenological data in Case 3.

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# BLOOD VOLUME STUDIES IN MIDDLE-AGED AND ELDERLY MALES

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RECENT reports of reduction in blood volume in patients suffering from chronic infections and malignancies<sup>1,6</sup> suggest the possibility of similar changes in individuals with chronic degenerative diseases. In reviewing the literature, however, no systematic studies of blood volume in normal elderly individuals could be found. The only study containing relevant data is that of Gibson and Evans,<sup>3</sup> who included measurements on 5 males above 50 years of age. Before conclusions concerning the effects of chronic degenerative diseases can be drawn it is necessary to know whether significant changes in blood volume occur with advancing age. The purpose of the present study was to gather data on plasma volume and total blood volume in elderly males exhibiting no clinical evidences of disease.

**Materials and Methods. BLOOD VOLUME STUDIES:** The blue dye T1824 (Wm. Warner & Co.) was used for measuring plasma volume, according to the method of Gregersen.<sup>4</sup> Optical density measurements were made on the Model 14 Coleman spectrophotometer at a wave length of 610 mμ. Serum was used for the colorimetric determinations instead of plasma in order to minimize hemolysis, since Gregersen and Schiro<sup>5</sup> found no significant changes in dye levels before and after coagulation of the blood. The total blood volume was calculated from the plasma volume and the venous hematocrit, utilizing a correction factor of 0.96 × hematocrit to compensate for plasma trapped among the cells.<sup>2</sup> Hematocrit determinations were done by the Wintrale method in which the specimens were centrifuged at 5000 rpm for 30 minutes.

**SELECTION OF SUBJECTS:** Subjects were selected from the population of the Infirmary Division of the Baltimore City Hospitals using the following criteria: All subjects were ambulatory, had no recent surgical operations, and were free from any acute or chronic infections. Individuals were, however, included who exhibited occasional coarse rales with some morning cough over a period of years (by history and notation in the medical record) indicative of chronic bronchitis, a common finding in the Baltimore area. None of the subjects showed any evidence of fluid retention, ankle edema, constant fine moist rales at the lung bases, enlarged liver or abdominal fluid. All patients with a history of liver disease, heart failure, or exertional dyspnea were excluded. Hypertension *per se* was not disqualifying. Individuals with arteriosclerosis in various forms and to varying degrees were included. None of the subjects tested was receiving medication of any kind.

To assure constancy of conditions, all acceptable subjects were transferred from the Infirmary Division to the Gerontology Ward of the Hospital the day before the test. All blood volume studies were made in the morning under basal conditions; that is, no food or fluids were available after 8 p.m. on the evening before the test; tests were run at 8 a.m. the following morning while the patient was still in bed, before breakfast was served. The height and weight (nude) of each subject were recorded immediately following the test. Plasma and total blood volume per kg. body weight were calculated for each subject.

**Results.** No evidence of change in plasma or blood volume per unit of body weight was found in observations collected on 60 male subjects between the ages of 50 and 90 years (Table 1). Plasma volume ranged from a minimum of 31.29 cc. per kg. in a person 77

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years old (Subject 30) to a maximum of 62.47 cc. per kg. in a 53 year old person (Subject 4). The range in total blood volume was from 54.33 cc. per kg. in a 77 year old man (Subject 30) to 100.60 cc. per kg. in a man of 71 years (Subject 43). A comparison of

the values obtained in the present study with the observations of Gibson and Evans<sup>3</sup> on young adults is shown in Fig. 1. Variations between subjects were large even within a single age decade.

No significant change with age was

TABLE 1.—PLASMA VOLUMES AND TOTAL BLOOD VOLUMES FOR 60 MALES ABOVE THE AGE OF 50 YEARS

Subject No.	Age Yrs.	Weight kg.	Height cms.	Plasma Volume cc./kg.	Total Blood Volume cc./kg.	Hematocrit %
1	50	59.54	157.48	57.40	98.18	43.1
2	57	61.36	170.82	49.29	84.12	43.3
3	55	56.59	157.48	44.95	77.77	41.0
4	53	65.91	164.47	62.47	96.23	36.6
5	56	47.50	157.48	54.86	92.53	42.1
6	50	78.41	173.99	49.18	82.29	41.1
7	57	62.27	168.91	37.72	70.90	48.8
8	67	74.09	169.55	45.11	78.18	41.1
9	68	54.32	157.48	55.11	87.37	38.1
10	68	47.72	—	42.33	82.35	50.6
11	68	57.86	165.10	58.57	96.65	41.0
12	64	63.41	161.29	38.72	68.77	45.5
13	63	87.95	173.99	41.38	67.29	40.1
14	65	47.60	153.67	51.58	83.19	39.6
15	63	75.46	175.26	53.81	86.39	40.0
16	64	65.46	179.07	47.68	76.17	39.0
17	61	66.14	166.37	40.12	68.36	43.0
18	68	66.36	163.83	56.10	81.31	32.2
19	61	56.82	167.64	41.22	76.12	43.6
20	64	65.00	168.28	40.52	70.97	41.7
21	61	63.64	161.29	39.97	67.52	42.5
22	69	68.64	158.75	43.27	71.85	41.0
23	67	71.82	168.28	32.48	60.83	48.5
24	65	82.27	177.80	51.79	81.49	40.3
25	64	70.91	169.55	56.64	99.18	41.7
26	73	59.51	157.48	40.11	72.72	46.7
27	71	50.91	161.93	48.22	94.93	51.2
28	78	62.27	165.10	53.89	85.00	38.1
29	70	51.59	163.56	44.79	77.35	43.9
30	77	82.27	167.64	31.29	51.33	41.2
31	70	74.09	171.45	41.85	71.66	43.3
32	72	56.11	163.83	51.00	92.00	43.0
33	71	52.27	160.02	51.79	87.18	42.3
34	75	49.77	161.29	52.09	89.83	43.7
35	78	45.68	165.74	41.22	76.12	43.6
36	70	63.63	160.66	41.87	71.68	39.0
37	70	56.36	163.20	41.06	75.09	43.1
38	70	51.51	142.21	51.91	97.89	45.7
39	76	60.45	157.48	42.22	74.32	45.0
40	71	63.18	165.10	45.35	79.83	45.0
41	71	77.50	160.02	50.58	79.78	38.1
42	70	50.45	153.04	48.80	81.32	41.7
43	71	60.00	165.10	59.78	100.60	42.3
44	79	61.32	167.64	43.89	71.95	40.6
45	83	73.86	163.83	38.13	—	—
46	81	61.09	160.02	50.10	82.09	39.50
47	82	55.45	166.37	46.25	76.72	41.10
48	82	65.23	166.37	38.45	60.39	42.9
49	88	50.00	151.91	60.56	93.48	36.1
50	87	61.36	151.31	49.12	82.28	42.0
51	83	66.36	165.71	50.91	81.56	39.4
52	85	61.11	160.66	47.25	76.16	39.5
53	82	68.40	168.28	40.71	61.66	35.4
54	81	55.23	166.37	55.46	87.88	35.4
55	85	57.05	166.37	46.52	81.28	46.7
56	85	64.77	173.99	53.05	84.47	35.7
57	86	57.50	172.72	56.21	98.13	44.7
58	87	45.00	157.48	51.82	94.35	43.6
59	87	55.23	157.48	49.42	79.71	40.0
60	90	40.91	163.56	60.30	98.53	40.4



found in mean plasma or blood volume in the present study (Table 2). Statistical analysis of the data from Gibson and Evans<sup>3</sup> also failed to demonstrate a significant change with age in younger subjects. However, the average values for plasma volumes obtained in the present study were slightly higher than those reported by Gibson and Evans (Present study,  $Mn=48.00$  cc. per kg.; Gibson and Evans,  $Mn=43.19$  cc. per kg.; difference= $4.81$  cc. per kg.  $t=3.57$ ).

In order to minimize factors contributing to lowered or increased blood volume, subjects were carefully selected. In addition to the problems of fluid retention, which lead to increased blood volume, every attempt was made to exclude any factor which might produce a lowered blood volume. Taylor *et al.*<sup>7</sup> observed a diminution in the blood volumes of normal young males during periods of prolonged bed rest. To obviate the possibility of this factor confusing the study, only ambulatory

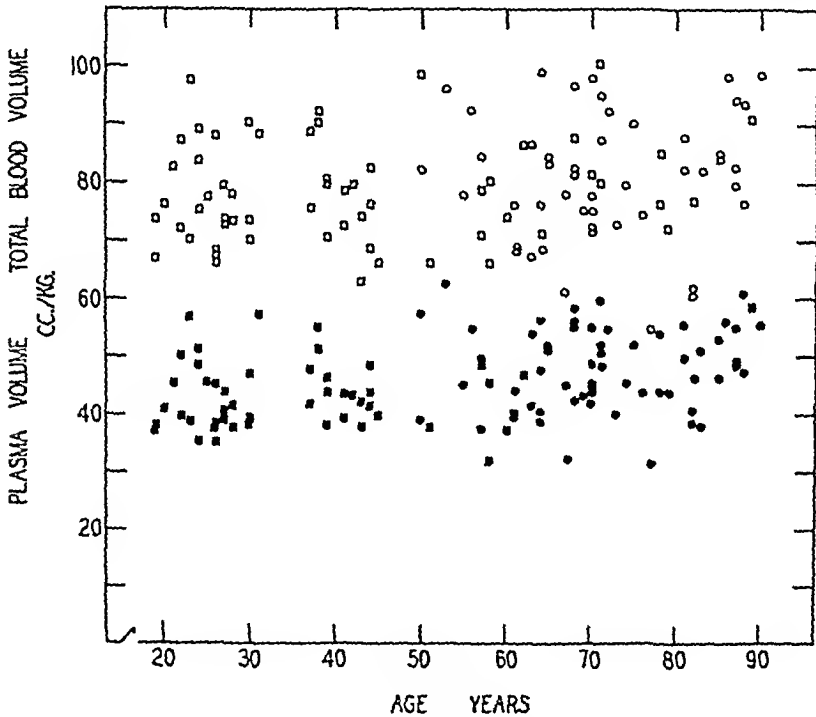


FIG. 1.—Total blood volumes, cc. per kg. and plasma volumes, cc. per kg. in 105 males.  $\square$  Total blood volume determinations from Gibson and Evans<sup>3</sup>;  $\blacksquare$  Plasma volume (Gibson and Evans<sup>3</sup>);  $\circ$  Total blood volume, present study;  $\bullet$  Plasma volume, present study.

**Discussion.** Gibson and Evans,<sup>3</sup> observing 5 males above the age of 50 years, state: "Analysis of absolute and relative volumes by decades . . . shows a tendency in both sexes for values to remain at or rise above the average levels in the series during middle life and to decline with advancing age." This is not in keeping with the findings in the present study in which no changes with age were observed.

subjects were used. The Infirmary population has, within the 6 months prior to the study, been surveyed roentgenographically for tuberculosis, and all patients with suspected active tuberculosis have been removed for further investigation along these lines. None was included in this study. As stated above, all subjects were hospitalized the night before determinations were made in order to make the condi-

tions surrounding the test as homogeneous as possible.

Since no systematic age trend was observed in either study, the slightly higher values obtained in the present study, as compared with the results of Gibson and Evans,<sup>3</sup> may be attributed to differences in technique. The pre-

Gregersen<sup>4</sup> were made on 60 normal males above the age of 50 years. The data obtained were analyzed statistically by decade subdivisions. Similar statistical analytic procedures were applied to data obtained from a study by Gibson and Evans<sup>3</sup> on individuals below the age of 50. No significant

TABLE 2.—STATISTICAL ANALYSIS OF AGE CHANGES IN PLASMA VOLUME, TOTAL BLOOD VOLUME, AND HEMATOCRIT IN MALES

	Data from Gibson and Evans <sup>3</sup>				Data from present study		
	19-29 yrs.	30-39 yrs.	40-49 yrs.	50-59 yrs.	60-69 yrs.	70-79 yrs.	80 plus yrs.
	Plasma volume cc. per kg.						
Mn	42.33	45.54	42.34	50.84	46.64	47.19	49.83
N.	21	11	9	7	18	19	16
S.D. distr.	5.57	5.38	3.04	7.61	7.27	6.39	6.70
S.D. mn	1.24	1.70	1.07	3.11	1.76	1.49	1.73
	Total blood volume cc. per kg.						
Mn	77.34	81.95	73.50	86.09	78.33	80.71	82.84
N	21	11	9	7	18	19	15
S.D. distr.	8.09	8.06	6.20	9.36	10.06	10.97	10.99
S.D. mn	1.81	2.54	2.19	3.82	2.44	2.55	2.83

vious investigations used the multiple sampling procedure,<sup>2</sup> whereas in this study the single 10 minute sampling technique was used.

**Summary.** Blood volume determinations utilizing the dye T1824 and the 10 minute sampling method of

changes in blood or plasma volume per unit body weight were observed with increasing age.

**Conclusion.** From the data presented it is concluded that plasma volume and total blood volume per unit body weight in males do not significantly change with age.

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# THE HEART IN FUNNEL-SHAPED AND FLAT CHESTS

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THE term funnel-shaped is used to describe the type of chest usually observed in persons of slight build and characterized by depression of the lower end of the sternum and the costochondral ends of the 4th to the 9th ribs. This results in a distinct diminution in the antero-posterior diameter of the chest at the level of the xiphoid process. Other terms for this deformity are, *trichterbrust*, *pectus excavatum* and *chone-chondrosternum*. The flat chest is one with a small postero-anterior diameter of the entire thorax. Both types of deformity are not uncommon and are often associated.<sup>24</sup> Although the heart is often shifted to the left, in the majority of patients symptoms are either absent or insignificant. However, symptoms and signs may be present and may simulate and must be distinguished from, organic heart disease, rheumatic or congenital.<sup>5,9,9,12,16,19a,b,25,31</sup> In rare instances the sternal depression is extreme, producing erosion of the vertebral column and right heart failure.<sup>11,20</sup>

**Material:** This report comprises a series of 25 patients with funnel or flat chest referred for consultation because of a presumptive diagnosis of organic heart disease. The latter was excluded in each case by means of physical examination, electrocardiogram, Roentgen-ray and fluoroscopic examination.

**Results.** An analysis of the findings is presented in Table 1. Although the ages ranged from 5 to 56 years, all but 3 of the patients were under 40. The average age was 29.5 years.

Men predominated 4 to 1, the same ratio as that reported among cases in the literature. However, the ratio is disproportionately high in our series since the majority of cases were seen in military service; of the 10 cases seen in private practice 6 were men. One other writer, Kuhns,<sup>16</sup> also noted a 1 to 1 ratio.

Four-fifths of the patients were of asthenic habitus, several being extremely tall and thin. None of the patients was obese or of the pyknic type. The chest was funnel-shaped in 16 patients and flat in 2. In the remaining 7 there was a combination of flat and funnel-shaped chest.

The majority of the patients were of a nervous temperament. Ten patients complained of both precordial pain and dyspnea; palpitation occurred in 6, dizziness and fatigue each in 4, joint pains and fainting twice. These symptoms have been observed by other writers.<sup>1,1,5,9,10,21,21</sup>

A loud systolic murmur was present in 60% of the cases and is a common finding.<sup>9,9,17,21,23,30</sup> In 2 cases the heart seemed enlarged in the postero-anterior view but this was disproven by study in the lateral and oblique positions (Fig. 1). The heart was definitely displaced to the left in 16 of the 25 patients. In 8 cases the left border of the heart was "straight" and in 10 the pulmonary artery segment appeared abnormally prominent (Fig. 2A,3), suggesting "mitralization."<sup>25</sup>

TABLE 1.—DATA ON 25 PATIENTS WITH FUNNEL OR FLAT CHEST

PHYSICAL EXAMINATION												
	Case	Age	Sex	Height (inches)	Weight (pounds)	Referred Reason	X-ray of Chest	Systolic Murmur	Blood Pressure	Heart Rate	Neurocirculatory Asthenia	Electrocardiogram
1	H C B	"	"	"	"	Enlarged heart.	normal.	-			-	Right axis deviation, abnormal P-waves.
2	T P	"	"	69	145	Enlarged heart.	Pul art. prominent	-	120/80	64	+	Negative.
3	C S D	32	M	73	190	Precordial pain.	Normal	-	118/60	76	+	Negative.
4	I C D	"	"	"	"	Precordial pain, Dyspnea.	Dizziness No x-ray taken	-			+	No electrocardiogram taken.
5	F M D.	22	M	63	155	None.	Apex displaced, pulm art. prominent	-	110/60	72	+	Right axis deviation.
6	M F.	34	M	69½	196	Precordial pain. Enlarged heart, joint pains.	Apex displaced, straight left border.	+	134/94		+	Negative.
7	J C G.	17	M	67	135	Fatigue	Apex displaced.	+	116/74	85	+	Right axis deviation.
8	J G.	21	M	70	150	Systol. murmur, Tachycardia.	Apex displaced, pulm. art. prominent, straight left border.			88		Negative.
9	D D L.	42	M	69	145	Systol. murmur, Dyspnea, Dizziness, Fatigue.	Apex displaced.	+	110/70	74	+	Negative.
10	J L.	18	M	69	160	Systol. murmur, Dyspnea, joint pains.	Apex displaced, straight left border.	+	130/80	80	-	Abnormal P-waves.
11	H C L	"	"	"	"	Systol. murmur.	Apex displaced	-	124/80	86	+	Right axis deviation.
12	C G S	25	M	71	166	Systol. murmur.	Apex displaced.	-	110/70	72	-	Negative.
13	J S S	38	M	75	155	Precord. pain, Dyspnea. Palpitation, Tachycardia.	Pul art. prominent, straight left border.	+	120/82		+	Right axis deviation.
14	M A V	32	M	70	140	Palpitation, Premature beats	Apex displaced, pulm. art. prominent.	-	130/80	85	-	Negative.
15	D K	24	F	66½	122	Systol murmur	Apex displaced, pulm. art. prominent, straight left border.	-		80	-	Negative.
16	A M C	5	M	47½	52	Systol murmur, Dyspnea, Enlarged heart.	Apex displaced.	+	94/54	76	-	Right axis deviation.
17	M P	37	F	62	132	Systol murmur, Precordial pain, Palpitation, Premature beats.	normal.	+	140/80	70	-	Negative.
18	A S.	33	F	64½	128	Precord. pain, Dyspnea.	Apex displaced, straight left border.	+	112/74	68	+	Negative.
19	F V.	28	F	61	87	Precord pain, Dyspnea. Palpitation, Fatigue.	normal.	+	142/80	66	+	Negative.
20	A S.	37	M	64½	120	Systol murmur, Dizziness	normal.	+	122/84	84	+	Negative.
21	P A.	56	M	65½	116	Precord. pain, Dyspnea.	Apex displaced, pulm. art. prominent.	-	130/70	72	-	Right axis deviation.
22	P H.	21	M	67½	116	Precord pain	Pul. art. prominent.	+	146/80	70	+	Negative.
23	H V.	41	M	73	172	Precord pain, Palpitation	Straight left border.	+	136/82	64	+	Abnormal P-waves.
24	I M.	22	F	71½	114	Systol murmur, Palpitation, Dyspnea, Dizziness, Fatigue, Tachycardia.	Apex displaced, pulm. art. prominent.	+	135/80	90	+	Right axis deviation.
25	A T	21	M	67	130	Systol murmur, Dyspnea, Tachycardia	Apex displaced, pulm. art. prominent straight left border.	+	116/76	95	+	Right axis deviation.

\* Anterior palpitation.

The electrocardiogram was usually normal, yet right axis deviation was present in 5 cases (Fig. 2B) and a tendency to it in 4. This incidence is greater than that found in normals for the age group of our patients. In normal persons without chest deformity in this age group there would probably be none with right axis deviation and a good many with left. In a number of electrocardiograms QRS was small in Lead 1 (Fig. 4). Left axis deviation was present only once. Cases 1 and 10 revealed large or notched P-waves in

ticularly chronic rheumatic valvular disease.

**Case Histories.** CASE 1. J.C.G., a young man, aged 17, was referred because of easy fatigability. Physical examination revealed a slender youth weighing 135 lbs. and 5 ft. 7 in. tall. There was a distinct depression of the lower portion of the sternum. A thrill was present and a short high-pitched systolic murmur was heard at the apex. A rough grating systolic sound was audible in the pulmonary area. The apex of the heart seemed to be shifted upward and to the left. This displacement was confirmed by roentgenographic examination (Fig. 2A). The electrocardiogram revealed right axis deviation; evidence of myo-

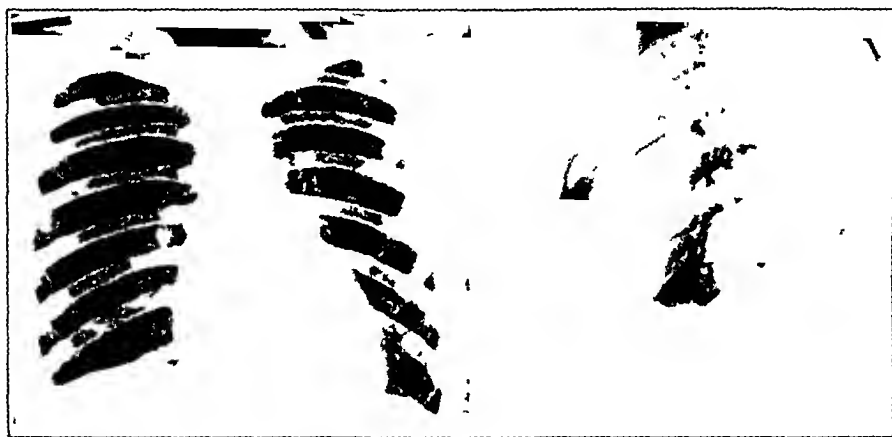


FIG. 1. (Case 22).—H. H., man, aged 21 years. The heart is round and full with a wide waist. It appears to be at the upper limit of normal in size, if not slightly enlarged. The lateral view shows the heart is in reality small and spread or "pancaked" out by the anterior chest wall and the depression of the lower portion of the sternum which almost touches the vertebral column.

Leads 2 and 3 (Fig. 2B, 4). Thus, the electrocardiogram is that seen in persons of asthenic habitus and in neurocirculatory asthenia.<sup>10</sup> The electrocardiogram in funnel chest has been reported normal or showing some degree of right axis deviation<sup>10,11,16</sup> or even left axis deviation.<sup>17</sup> Grieshaber<sup>15</sup> in addition found changes in the T-wave in Leads 2 and 3. Teplick and Drake<sup>21</sup> reported minor changes in the chest leads. Premature beats, sinus arrhythmia and other irregularities occur occasionally.<sup>10,17-21,29</sup>

The following brief case histories are typical and illustrate the importance of the differential diagnosis of funnel chest from organic heart disease, par-

cardial involvement was not present (Fig. 2B).

The asthma of this patient, the systolic murmur and thrill at the apex, the rough systolic murmur over the pulmonary area and the right axis deviation were attributed to the marked funnel-shaped depression of the sternum with displacement and rotation of the heart.

CASE 2. J.S.S., a man, aged 33, was referred because of sharp precordial pain, shortness of breath and episodes of rapid beating of the heart. Physical examination revealed a very tall, thin man 155 lbs. in weight and 6 ft 3 in. in height. The chest was flat with a depression of the lower three-fourths of the sternum. A short systolic murmur was heard at the apex; the second pulmonic sound was accentuated. The blood pressure was 120/82 mm. Hg. Fluoroscopic and roentgenographic examination of the chest showed straightening of the left border of the heart and prominence



FIG. 2A

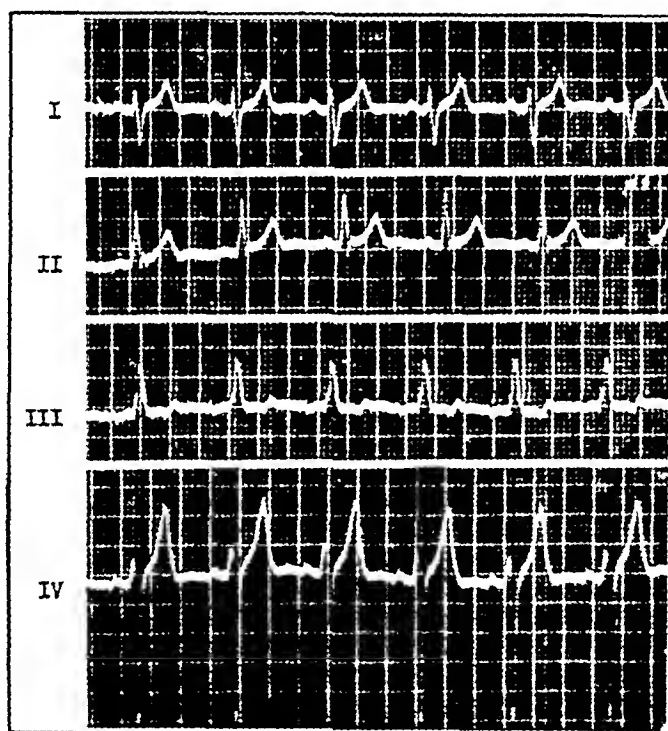


FIG. 2B

FIG. 2A. (Case 7).—J. C. G., boy aged 17 years. The teleroentgenogram in the postero-anterior position (left) shows the diaphragm low in the thorax and the heart and apex shifted to left. The left border of the heart is straightened and the region of the pulmonary artery is prominent. The right border is hidden by the vertebral column. The lateral view (right) shows the depression of the lower half of the sternum and the narrow antero-posterior diameter of the chest. The heart is small. FIG. 2B.—The electrocardiogram shows a normal sinus rhythm, rate about 90-95 beats a minute, with a right axis deviation of the QRS. The P (auricular) wave in Leads II and III are small, but wide and polyphasic.

of the right border. The resting electrocardiogram revealed right axis deviation.

The dyspnea, precordial pain and paroxysmal tachycardia were explained by the not uncommon association of these disturbances with flat and funnel-shaped chest and with neurocirculatory asthenia.

CASE 3. D.R., a woman, aged 24, had been refused admission to the Army Nurse Corps because of a systolic murmur over the pulmonic area. Physical examination revealed an asthenic woman, 122 lbs. in weight and 5 ft. 6½ in. in height. A funnel-shaped depression of the sternum was present. A harsh blowing systolic murmur was audible in the pulmonic area. Fluoroscopic and roentgenographic examination of the chest showed the heart shifted to the left and its left border straightened. The pulmonary artery segment was prominent. In the lateral position the anteroposterior diameter of the heart was seen to be small. The electrocardiogram showed left axis deviation. QRS-I was slightly slurred and notched and T-3 was inverted but there was no evidence of myocardial involvement.

The systolic murmur was explained by the funnel-shaped depression of the sternum which caused the shift of the heart to the left, the straightening of its left border and the prominence of the pulmonary artery segment.

CASE 4. F.S., a woman aged 28, was referred because of dyspnea on exertion and following excitement, palpitation of the heart and nervousness. Physical examination revealed a thin woman weighing 87 lbs. and 5 ft. 1 in. in height. At the lower end of the sternum there was a funnel-shaped depression. At the mitral and apical regions a blowing systolic murmur was heard. The first heart sound was strong but the second pulmonic sound was not accentuated. The blood pressure was 130/74 mm. Hg. The teleroentgenogram and fluoroscopy disclosed a heart somewhat smaller than normal. The electrocardiogram showed a tendency to left axis deviation.

The symptoms and signs were due to neurocirculatory asthenia in a person with a small heart and funnel-shaped depression of the chest.

CASE 5. H.H., a man, aged 21, complained of pain in the chest and inability to perform moderate physical exertion. Physical examination revealed a thin, tall man of 118 lbs. weight and 5 ft. 8 in. in height. The chest was flat and the lower end of the sternum was depressed. A short systolic murmur was heard at the apex, and the second pulmonic sound was accentuated. The blood pressure was 146/80 mm. Hg. Roentgenographic ex-

amination of the chest in the postero-anterior view revealed an apparently full-sized, globular heart. On fluoroscopy the pulmonary artery was prominent in the right oblique position, the lateral views showed that the heart was small, being "pancaked" to the right and left by the pressure of the sternum (Fig. 1). The electrocardiogram was normal.

The occurrence of chest pain in a thin young adult with a systolic apical murmur, marked accentuation of the second pulmonic sound, a heart pancaked in the center and a prominent pulmonary artery segment can be explained by the presence of a flat chest with a funnel-shaped depression of the sternum.

Discussion. Funnel chest has been attributed to various etiological factors. Numerous authors<sup>2,3,5,7,8,9,32</sup> take it to be the result of intra-uterine arrest of development of the sternum. Others believe it is familial<sup>23,24</sup> or attribute it to a development defect with abnormal lengthening of the ribs,<sup>11</sup> to bad posture,<sup>10,24</sup> rickets,<sup>5,10,16,24</sup> poliomyelitis,<sup>5,10</sup> syphilis,<sup>16</sup> tuberculosis<sup>5,10</sup> or trauma.<sup>8,24,32</sup> Evans<sup>9</sup> quotes Laennec as attributing it to cobbling shoes. It has also been considered a constitutional defect in the asthenic habitus, as is seen in neurocirculatory asthenia.<sup>20</sup> Grodel<sup>12</sup> in 1911 pointed out the similarity of symptoms in persons with neurocirculatory asthenia and funnel chest. Humberd<sup>14</sup> found this defect in tall, thin, nervous persons. Kuhns<sup>16</sup> stated that funnel chest was never seen in asthenic persons although exceptions have been noted.<sup>24</sup> In our series of patients none gave a history of rickets, poliomyelitis or congenital anomaly. We are of the opinion that funnel chest is a constitutional, familial defect associated with asthenic habitus. As in neurocirculatory asthenia the symptoms in funnel chest are neurogenic or the result of inadequacy of the small heart in its response to emotional and physical stress.<sup>6,20,33,34</sup>

Humberd<sup>14</sup> believed the most significant disability of funnel chest to be the psychological factor. Sixteen of our patients were labeled neurocirculatory asthenia. Wolf<sup>33</sup> believes that the low

position of the diaphragm in funnel chest accounts for the dyspnea.

The symptoms in funnel chest and in neurocirculatory asthenia, *i.e.*, precordial pain, dyspnea, dizziness, palpitation and fatigue, are common in functional disturbances of the heart. They often can be differentiated from similar complaints in organic heart disease; for example, the pain is usually diffuse, long-lasting and not related to effort. In both funnel chest and neurocirculatory asthenia the presence of tachycardia and arrhythmias, apical systolic murmurs, straightening of the left border of the heart, prominence of the

may create an illusion of enlargement by bringing the right border into line with the vertebral column<sup>25</sup> (Fig. 3). Accentuation of the shadows of the right lung root may suggest pulmonary congestion, pneumonitis or a tumor (Fig. 3). The cloudiness in the medial aspect of the lung is probably caused by the sternal depression<sup>25</sup> (Fig. 3) which also distorts the ribs so that they slant more sharply than usually<sup>13</sup> and the lower ribs are abnormally long.<sup>35</sup> The diaphragm is low (Figs. 2A, 3). The heart is flattened and appears less dense.<sup>8,9,25</sup> (Fig. 1). The aortic knob

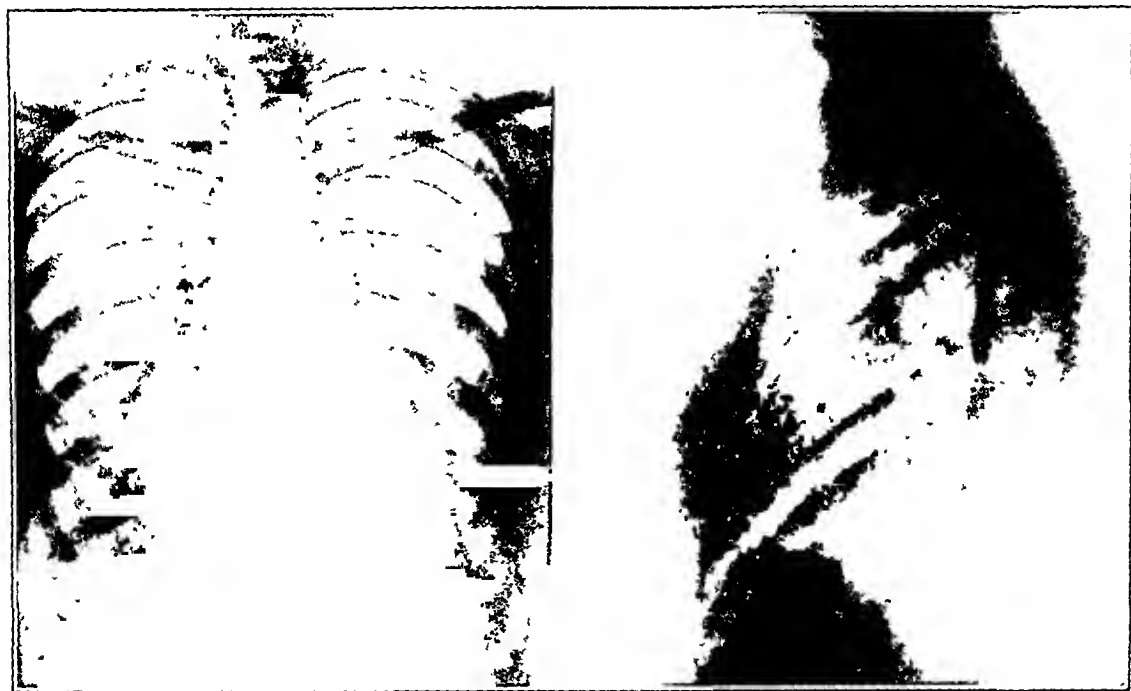


FIG. 3. (Case 15).—D. R., woman, aged 21 years. The teleroentgenogram shows the diaphragm low in the thorax and the heart and apex shifted to the left. The left border of the heart is straight with fullness in the region of the pulmonary artery. The right border of the heart is lost in the vertebral column. The right hilar shadows are very prominent and the density of the lung appears to have increased at this point. In the lateral view the depression of the sternum is clearly seen, narrowing the antero-posterior diameter of the chest. The heart is small.

pulmonary artery and the finding of right axis deviation and P-wave and T-wave changes in the electrocardiogram add to the simulation of rheumatic valvular or congenital heart disease. The left auricle is normal in funnel chest, whereas it is usually enlarged in rheumatic heart disease. Under roentgenological examination in funnel chest the displacement of the heart to the left

may be obliterated and in the oblique or lateral positions the retrocardiac spaces are obliterated<sup>9</sup> (Figs. 1, 2A, 3). Rarely the heart is displaced to the right<sup>24</sup> and in one case<sup>22</sup> the heart was in the right chest cavity. Awareness of all these effects of funnel chest and careful roentgenological examination make the differential diagnosis from organic disease obvious.



In rare instances the pressure of the sternum against the heart is so severe as to erode the thoracic vertebrae. Humbert<sup>14</sup> and Sweet<sup>30</sup> mentioned instances in which the sternum touched the vertebral column. There may be mechanical pressure on the right auricle and ventricle, the pulmonary artery, the aorta, and the inferior vena cava. Farmer<sup>10</sup> described right-sided enlargement. Levine<sup>18</sup> was of the opinion that heart failure is rare but that it may result from mechanical factors such as kinking or constriction of the large vessels leading to or from the heart, or from changes in the lung. The heart may be "pancaked" that is, flattened out, instead of displaced to one side or the other (Fig. 1). Brown<sup>3</sup> stated that the greatest cardiac embarrassment appears when the heart is fixed near the midline and is directly compressed by the depressed sternum. Pressure on the pericardium may produce milk spots. The vital capacity may be diminished. Kuhns<sup>16</sup> and Farmer<sup>10</sup> found the lung volume reduced. Others<sup>16,24</sup> have described interference with the mechanism of respiration when the diaphragm is low.

The patient with funnel-shaped or flat chest may, of course, develop organic heart disease like any other person. When this occurs the deformity may aggravate the cardiac disability.

The diagnosis of funnel chest may be made by inspection and roentgenographically. The patient is usually of slender build and the recession of the lower portion of the sternum is apparent (or in a flat chest the entire thorax is narrow). The apex of the heart may be displaced to the left and perhaps elevated. Evans<sup>9</sup> is of the opinion that a diagnosis of funnel chest should be made in adults only when the external postero-anterior diameter of the chest measures less than 6½ inches. He obtained this figure after studying normal chests in which he found the diameter never less than 7

inches and the average 7¾ inches. According to criteria of Kuhns<sup>16</sup> the ratio of the side to side diameter to the postero-anterior diameter should be more than 2.5 to 1; the ribs are relatively long and slender; the anterior arcs slant down sharply (the subcostal angle should be less than 90 degrees); the angle of Louis is less than 170 degrees, instead of being in a straight line, and the diaphragm is usually low. Paul and Richter<sup>25</sup> confirm the foregoing and suggest that in the postero-anterior Roentgen-ray view search should be made for the following: displacement of the heart to the left with a tendency to "mitralization," indistinctness of the right heart border which becomes lost in the shadow of the spine, decreased density of the heart shadow with corresponding increased visibility of the spine and cloudiness of the medial aspect of the right lung due to compression of the lung by the depressed sternum.

When a patient with funnel chest presents dyspnea, palpitation and precordial pain based on autonomic imbalance or neurocirculatory asthenia, encouragement may prove to be the only treatment needed. Teplick and Drake<sup>31</sup> pointed out that usually no treatment is necessary although rarely corrective exercises have been recommended.<sup>17,22,29</sup> The necessity of resorting to surgery is extremely rare.<sup>12</sup> Successful operations have been reported<sup>21,23,27,33</sup> and Ochsner and DeBakey<sup>24</sup> and Phillips<sup>26</sup> advise operation in severe cases. Humbert<sup>14</sup> recommended the administration of vitamin E, the avoidance of fatigue, exercise and correct posture.

**Summary.** The incidence of flat and funnel-shaped chests is greater than is generally recognized. The two deformities often coexist.

Organic heart disease was not present in 25 consecutive patients with this deformity who were referred for consulta-

tion because of cardiovascular signs and symptoms. These included a systolic murmur at the mitral and apical regions, precordial pain, shortness of breath, palpitation, dizziness, fatigue, joint pains and fainting spells, in the order of their frequency. A moderately loud systolic murmur at the apex was heard in the majority of the patients.

Many persons, if not the majority, with funnel chest have no complaints; when symptoms and signs occur they

funnel-shaped chest may also simulate congenital heart disease, pulmonary neoplasm, pulmonary congestion or pneumonia.

The etiology of funnel chest has been attributed to various factors and diseases but it is probable that in the vast majority of cases it is a constitutional defect in persons of asthenic habitus.

Rarely in the funnel-shaped chest there is extreme depression of the lower end of the sternum. Failure of the

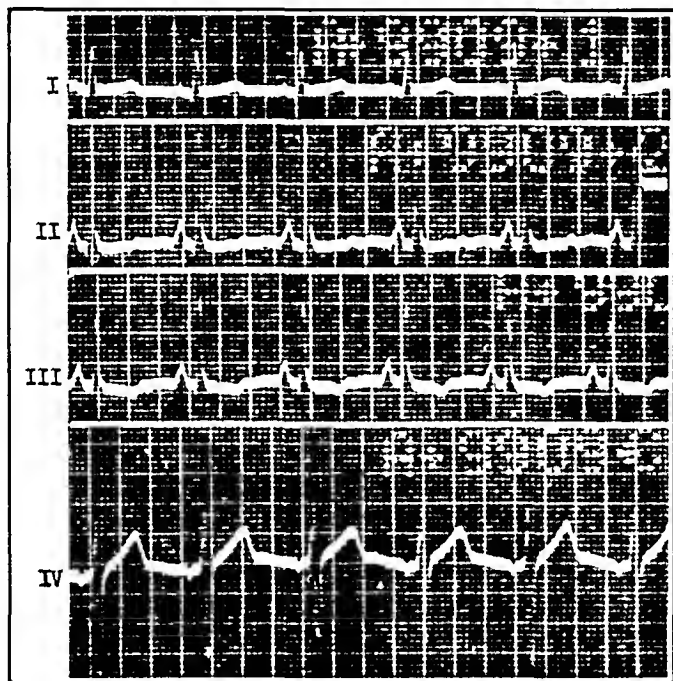


FIG. 4.—C. K. C., a tall, thin man of 43 years with a funnel-shaped depression of the lower sternum. A systolic murmur was present at the apex. The P (auricular) waves in Leads II and III are tall. The R wave in Lead I is small relative to the height of the R wave in Leads II and III. T<sub>2</sub> is semi-inverted and T<sub>3</sub> inverted.

are usually functional and are similar to those observed in neurocirculatory asthenia or autonomic imbalance.

Rheumatic mitral valvular heart disease was the most frequent erroneous diagnosis, since systolic murmurs, straightening of the left border of the heart or prominence of the right border and the pulmonary artery were present in most of the patients. Furthermore, right axis deviation and abnormal P-waves were not uncommon in the electrocardiogram. Occasionally T-II and T-III were inverted.

The signs in a person with a flat or

right side of the heart may occur, usually from pressure on a large vessel entering or leaving the heart.

The diagnosis of a flat or a funnel-shaped chest may be made by inspection of the patient from the side. Roentgenograms and fluoroscopy of the chest afford confirmatory evidence. The ordinary postero-anterior six foot Roentgen-ray film may miss the deformity.

Reassurance is usually the only treatment necessary. Surgical intervention is not indicated except under most exceptional circumstances.

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# THE VALUE OF THE LABORATORY IN THE DIAGNOSIS OF POLIOMYELITIS

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WITH the approach of the poliomyelitis season each year the practicing physician looks to his colleagues in the field of epidemiology for new ideas to guide him in his clinical approach to this frightening disease. Each year knowledge accumulates, progress is made, and yet the goal remains elusive. Research in this disease has taken many courses and it would be idle to dwell further on these except to state that not infrequently the directions taken have proved tangential to the overall problem and have thus lost their ultimate value.

It is our opinion that today's ultimate in information regarding this disease can be obtained only in those centers where there exists teamwork between the practicing physician, the fever hospital, the virology laboratory, the public health investigator, and the research facilities of the medical school. Only under such ideal circumstances can an outbreak of poliomyelitis be studied to yield the greatest amount of factual data.

Unfortunately, one or several of these components is too often missing, and the report of an outbreak tells only a fraction of the story. Correlation of clinical material with laboratory data has often meant requesting aid from distant and frequently overburdened viral laboratories. This has proved difficult regardless of the highly cooperative spirit existing in these centers.

The urgent need for laboratory collaboration was vividly brought home to us during an outbreak of anterior poliomyelitis occurring in the late summer and fall of 1947 in the Milwaukee area. Eighty-seven patients required hospitalization at the South View Hospital in Milwaukee during this period.

Although the signs and symptoms showed some deviation from those seen in previous epidemics, the predominant factor was the absence of paralysis in all cases. The seasonal incidence of this outbreak concurred with that of previous epidemics. There were no deaths attributable to the disease, and autopsies of patients who expired in the hospital during this period revealed no pathologic changes characteristic of poliomyelitis.

In this epidemic skeletal muscle involvement was limited to varying degrees of spasm. The severe cases were relieved simply by the application of hot compresses during the usual 14 days of hospitalization; ten cases required further similar treatments at home for periods of one to three weeks. This is in direct contrast to our experience of former years where severely afflicted patients were transferred to other institutions for continuation of their long periods of convalescence and physical therapy.

Epidemics of poliomyelitis appear to vary as to the clinical manifestations which predominate during each out-

break. This is illustrated by a comparison of the following charts which include the epidemic years of 1937, 1946, and 1947.

The year 1937 was selected for comparison because it presented a rather typical picture of a moderate poliomyelitis outbreak with mean percentages of deaths, residual paralysis, and non-paralytic cases. The year 1946 was felt to be important for comparison because of the wide variation of case types from that of the subsequent year, 1947.

TABLE 1.—PREDOMINANT SYMPTOMS

		Percent	
		1937	1947
Fever	69.6	92.1	90.8
Nausea and vomiting	42.1	32.5	75.8
Headache	62.7	30.2	87.3
Neck and back rigidity	63.7	70.2	86.2
Irritability	61.8	29.3	35.6
Lethargy	44.1	6.5	44.8
TOTAL CASES	102	215	87

Table 1 indicates the predominance of fever, nausea and vomiting, headache, and rigidity of the back and neck in the 1947 series of cases. Severe headache was such a prominent feature of the 1947 outbreak alone that we feel it requires special emphasis. Lethargy was as prominent in 1947 as in 1937, but was almost absent in 1946.

The admission spinal fluid cell counts as compared in Table 2 signify a somewhat greater cellular response in the 1947 series.

The distribution according to sex, as shown in Table 3, reveals no significant variation.

The distribution by age groups indicates that approximately three-fourths of the patients in each series were in the age group below 16 years. In 1947 there was a slight increase in the number of adults over 31 years of age who were afflicted.

Table 5 confirms the absence of skeletal muscle involvement in 1947 as previously stated. The spasm was almost fleeting in some instances, lasting only a few hours, while in others it was

more persistent. There were 3 patients with soft palate weakness of a transitory nature.

Personal communications from pediatricians in the Milwaukee area during the 1947 epidemic revealed that many patients presented symptoms of nausea, vomiting, mild headache, low-grade fever, and malaise. The duration of symptoms was relatively short, 12 to 24 hours, and the picture simulated that of mild cases admitted to the hospital. This suggests that the epidemic included many other cases not admitted to the hospital. Although an investigation was undertaken to determine the rather unusual nature of this outbreak, unfortunately facilities for the isolation of virus strains were not available.

Agglutination studies on 8 sera samples obtained 6 weeks after the onset of symptoms were reported negative for choriomeningitis, St. Louis encephalitis, and equine encephalomyelitis. We are indebted to Dr. Charles

TABLE 2.—INITIAL SPINAL FLUID CELL COUNT PER CC.

		Percent	
		1937	1947
Under 10 cells	5.9	8.4	4.6
10 — 49	32.4	32.2	34.5
50 — 99	26.5	25.2	13.8
100 — 199	22.6	21.6	22.9
200 — 299	11.7	7.6	11.5
300 — 399		1.8	2.3
400 — 499			4.6
500 — 599	0.9		1.2
Over 600		0.4	2.3
Bloody specimens		2.8	2.3

Armstrong of the National Institute of Health, Division of Infectious Diseases at Bethesda, for his kind cooperation and laboratory aid. Tests for antibodies against poliomyelitis were omitted, and single convalescent samples give insignificant results.

Discussion. Our data reveal that 87 cases of suspected anterior poliomyelitis were admitted in 1947 to the South View Isolation Hospital of the Milwaukee Health Department. The symptoms presented fulfilled the criteria neces-

sary for a diagnosis of poliomyelitis. The histories, physical examinations, sedimentation rates, and spinal fluid findings were consistent with the diagnosis.

In October certain evidence came to light which gave rise to the question of the presence of an entirely different entity. The chief factor, inconsistent with the diagnoses, was the absence of residual paralysis and black muscle spasm. In no case was it necessary to apply hot compresses after the third week following discharge from the hos-

TABLE 3.—DISTRIBUTION ACCORDING TO SEX

	1937	Percent 1946	1947
Male	54	111	48
Female	48	104	39
TOTAL CASES	102	215	87

pital. No cases required further hospitalization or physical therapy following discharge from the isolation hospital, with the exception of an 18 month old non-resident baby with deltoid paralysis. This case was omitted from the data due to its origin outside the Milwaukee area.

Although the spinal fluid reaction was consistent with the diagnosis, the clinical picture challenged it. We, therefore, reviewed the 1937 and 1946 series. A comparison of the 3 series revealed a higher incidence of nuchal rigidity and headache in the 1947 series, giving rise to the possibility of encephalitis or encephalomyelitis instead of poliomyelitis.

It is quite evident from the data at hand that we are assuming the presence of poliomyelitis in our community. It is also evident that certain additional factors must be considered: (1) The presence of an attenuated or unusual virus strain; (2) The existence of partial immunity; and (3) The possibility of an entirely unrelated encephalomyelitis.

Not until adequate laboratory facilities are made available will further epi-

demiological studies of this nature be conclusive. It is our opinion that progress toward the eradication of at least the killing and crippling aspect of this disease will stem to a large extent from more comprehensive studies of the nature of the organism itself and the immunological reactions it produces. A network of viral laboratories with well-trained personnel serving at least

TABLE 4.—DISTRIBUTION BY AGE GROUPS

	1937	Percent 1946	1947
0 — 5 years	35.3	31.2	26.4
6 — 10	26.5	26.1	27.6
11 — 15	17.7	21.9	20.7
16 — 20	7.8	8.8	5.8
21 — 30	3.9	7.8	8.0
31 and over	8.8	4.2	11.5

the more densely populated communities must be developed if rapid progress is to be achieved. The absence of such a laboratory in a community frequently places the practicing physician in the unhappy position of entire dependence upon clinical signs and symptoms so often resulting in the diagnosis of "One of those virus affairs."

Our experience in the 1947 outbreak of a disease we have chosen to call non-paralytic poliomyelitis served as an example to us of how important was the need for virology laboratories. Techniques for the identification of many viruses have in recent years become applicable to the less elaborate

TABLE 5.—DISTRIBUTION OF PARALYTIC AND NON-PARALYTIC

	1937	Percent 1946	1947
Paralytic Cases	78	121	0
Non-paralytic Cases	24	94	87
TOTAL CASES	102	215	87

laboratories. This advance has placed the viral laboratory in the category of a working counterpart, rather than an expensive and impractical luxury for every sizable fever hospital throughout the country.

It is our hope to establish such a viral laboratory at the South View Isolation

Hospital within the near future. We thus hope to obviate the impracticability of burdening distant laboratories with material which at present must be minimal and delicately handled and often unsuitable for research value.

With such an addition to this institution we feel we will be in a position to serve better the almost one million population of the Milwaukee Area and to contribute materially to the advancement of knowledge concerning poliomyelitis and other viral diseases.

Summary. 1. An outbreak of a disease resembling poliomyelitis occurred in the Milwaukee area during the summer of 1947.

2. This disease varied in certain unusual respects from the "typical" poliomyelitis outbreaks seen in previous

years and was strikingly different from the outbreak seen the year before.

3. Sera from afflicted patients of the 1947 outbreak did not reveal the presence of several types of encephalitis in this group. However, no studies could be made of the stools of these patients for the presence of the poliomyelitis virus.

4. The need for facilities to study patients for the presence of poliomyelitis and other viruses exists in most fever hospitals throughout the country. Southview Isolation Hospital in Milwaukee is no exception to this need.

5. The authors believe that when the viral laboratory becomes an active part of most fever hospitals, definite progress will be made in the study of the nature of poliomyelitis and the answers to its protean nature.

# ELECTRO-NARCOSIS: RESULTS IN 125 PATIENTS WITH PSYCHOSIS OR PSYCHONEUROSIS

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(From Longview State Hospital)

ELECTRO-NARCOSIS is the word used to designate a state of unconsciousness or semiconsciousness produced by passing an electric current through the brain. The term was introduced by the French worker Leduc in 1902<sup>2</sup> in describing early experiments with such technique. Van Haareveld with various co-workers reported experiments in animals with electrically induced alteration of consciousness in 1934 and again in 1942 and 1943.<sup>4</sup> The first experiments in man were reported by Frostig, van Haareveld, Resnick, Tyler and Wiersma in 1942.<sup>1</sup> The real

types; manic depressive psychoses; involution psychoses; psychoneuroses with chronic compulsive anxiety; and a few in scattered other groups chiefly for experimental reasons.

TECHNIQUE. The technique of Tietz is followed in detail. Patients are treated in the fasting condition; a small amount of fluid before the treatment is considered permissible, however. Bladder and bowel should be empty. The patient lies on a bed or table. A pillow is put lengthwise under the back from lumbar to cervical regions. Placement of the electrodes is critical. We use the external auditory meatus and the zygomatic arch as reference points and place the electrodes

TABLE 1.—NUMBER OF TREATMENTS OF ELECTRO-NARCOSIS GIVEN TO 125 PATIENTS

	Number of Patients	Total Treatments	Average Number of Treatments per Patient
Group A—State Hospital Patients	43	1038	24
Group B—Author's Private Patients and those treated for other physicians	82	1533	19
TOTALS	125	2571	

impetus to this work was given by the report of Tietz and her co-workers in 1945. Since then other reports have been made by Tietz on a larger group of patients and by workers from England on initial studies.<sup>3a,b</sup>

This report deals with the first two years' experience of the author and those working under his direction in giving electro-narcosis to 125 patients (Table 1). With few exceptions, the patients had all been subjected to other forms of treatment which had produced little or no improvement and were in the poor prognostic situation of having been ill for long periods. The diagnostic groups treated were chiefly schizophrenia, paranoid and catatonic

with the posterior edge of the electrode 2 inches (5 cm.) anterior to the external auditory meatus, and the inferior edge of the electrode 1½ inches (3 cm.) above the zygoma. If the patient shows during the treatment any respiratory difficulty, the electrodes are advanced to a position 2½ or 3 inches forward from the meatus in subsequent treatments; if there is too much restlessness, a more posterior position is used. The position of the electrodes is marked with a pencil and ruler before application of the electrode paste, after which the electrodes are put in position and held down by a rubber band similar to that used in electroshock treatment. It is usually advisable to use an absorbing insulator of gauze or paper towel under the band over the forehead to avoid current being shunted across the electrodes by a layer of perspiration. The usual safeguards for the tongue, gauze or rubber, are then placed in position, and in addition a



rubber airway of suitable size is partially inserted between the gauze or rubber props (we never use the word "gag"). The airway should be of suitable size to avoid injury to pharyngeal structures which may cause hemoptysis. At this point, 0.25 to 0.40 gm. of pentothal sodium is injected intravenously rapidly. Within 5 to 15 seconds the patient falls deeply asleep and within a few more seconds becomes apneic. The apnea lasts from 15 to 40 seconds. Then after 3 or 4 breaths, preferably of 5% CO<sub>2</sub> in O<sub>2</sub>, the current is applied through the electrodes.

On a suitable chart are recorded at 15 second intervals the milliamperes of current used in each treatment. There are also recorded the muscle tension, state of respirations and any other pertinent data. The initial current level of 150 to 350 m.a. is not applied in full force instantaneously with the throwing of the switch. It is gradually raised from zero to the peak level over a period of 2.5 to 5 seconds, preferably with an automatic electronic control, but a skillfully handled manual control will do as well. To this slow initial current rise, Tietz has applied the term "glissando" borrowed from the musical lexicon. With the slow initial rise of current the body musculature is not jolted to sudden maximal tonicity, but is brought gradually to maximum tone with less danger to skeletal integrity. After a few seconds, if the current level is adequate, a general extensor movement of the musculature is seen. This is the signal that a major epileptiform seizure has been produced. If it fails to occur by 10 to 12 seconds, the experienced operator raises the current level manually to produce the desired effect. Then after 5 to 10 seconds the current level can be dropped more or less gradually to reach a level of 50 to 60 m.a. between 25 and 40 seconds from the onset. During this process the end of the epileptiform seizure should be evident in the occurrence of softened clonic movements. At the end of this seizure the patient may breathe immediately or after varying periods of apnea. At this point, the assistant inserts the airway completely and starts continuous suction of oral and pharyngeal secretions through suitably placed rubber catheters and administration of 5% carbon dioxide and oxygen through a mask.

Apnea should cause no concern until 60 seconds have passed, since the carbon dioxide and oxygen can be administered through the airway under positive manual pressure from the rebreathing bag. Cause of persistent apnea should be evident to the experienced operator. It is usually persistent tonicity of the respiratory muscles and can be quickly relieved by dropping the current to 25 or 30 m.a. for a few seconds, and then returning it to 50 m.a.

when respirations start. Excessive difficulty of this variety is the chief reason for more anterior placement of the electrodes. The skillful worker can often move the electrodes quickly during the treatment but this is not a procedure for the beginner. If the patient does not respond quickly to current manipulation, the treatment should be stopped and tried another day with proper change in electrode placement.

Between 45 and 75 seconds, as a rule, respirations are well established. The patient at this point is usually flaccid. The current should then be gradually raised, 5 or 10 m.a. every 15 seconds, to the point at which strong ("4 plus") flexor rigidity of the arms is obtained, usually between 2.5 and 4 minutes. In some patients marked extensor tone precedes the flexor rigidity for varying periods. The end point of useful tone is indicated by laryngeal inspiratory stridor. This cannot be allowed to become severe and interfere with respiratory exchange. The occurrence of inspiratory stridor is often preceded by a period with expiratory grunt which is harmless. During the presence of maximum tone and regular respiration the patient is relatively quiet and may be considered to be in an adequately narcotized state. At this level, fine clonic movements or tremors of the legs and more rarely arms may be observed. The tonicity noted in the arms does not always involve the legs, which may be almost flaccid.

If the initial seizure is inadequate, or if the current is not properly raised to an adequate level, or if the electrodes are placed too far anterior, the patient may show semi-voluntary movements of resistance and inadequate unconsciousness (as usually indicated by his subsequent complaint). Such restlessness during the treatment is considered undesirable and the patient cannot be said to have an adequate electro-narcosis.

The proper current level is maintained until 7 minutes from the beginning of the treatment in most patients. The current may then be abruptly turned off as was described in the original technique. The author believes, however, that gradual dropping of the current to zero over a period of 2 to 4 minutes is desirable because this produces in most patients a state of flaccid relaxation which is the complete antithesis of the pathologic tension for which they are being treated and which is, therefore, considered beneficial. The tonic level can be safely maintained in most patients for much longer than 7 minutes but only in a few patients refractory to treatment, has this been found useful or necessary.

After the current is turned off the patient usually appears to be in a natural sleep. Remaining excessive secretions in the mouth and throat are aspirated and several extra

breaths of carbon dioxide and oxygen are allowed. Patients remain asleep for varying periods, from 10 minutes to 2 hours. After 10 minutes practically all can be aroused and all are oriented for time, place and person, and have only minimal, if any, memory defect until many treatments (at least 15 or 20) have been given. Most private patients can be returned to open medical floors or home to their families within one hour. State Hospital patients can be returned to "home" wards or to various occupations with which they may be entrusted usually in less than one hour.

**PHYSIOLOGIC CHANGES.** Numerous and various physiologic changes take place during this treatment. The chief neurologic changes have been described. Electro-encephalographic changes are less marked than with classic elec-

3 minutes, 270/170 at 5½ minutes, 270/? at 7½ minutes and 230/120 at 8 minutes, which was 15 seconds after the current was turned off. Rise in blood sugar and leukocytes is further evidence of adrenergic activation. Marked perspiration and salivation are practically invariably present. We have not seen, during the treatment, involuntary urination or defecation, or seminal emissions. Nausea may follow the treatment if the patient has improperly eaten a large meal; but this is unlikely if no more than a small amount of liquid food is ingested. We have observed no fractures in our cases and to date there have been no deaths

TABLE 2.—RESULTS OF ELECTRO-NARCOSIS TREATMENTS

	Private Patients*				State Hospital Patients§			
	A	B	C	D	A	B	C	D
Involution psychoses								
Melancholia	1					1		
Paranoid type	1					1		
Psychoneuroses	3	2						
Manic depressive	4	6	4		1	2	1	1
Schizophrenia								
Hebephrenic			3	1		1	4	3
Catatonic	2					1	1	1
Paranoid	1	8	2		2	6	5	1
Other groups		1	1				1	1
TOTALS	12	17	10	1	3	12	12	7

\* 6 patients incomplete (private)      § 9 patients incomplete (State hosp.)

A: Complete remission; B: "Social" recovery; C: Improved; D: Unimproved.

troshock. Psychologic studies show less "organic" impairment of function after treatment than after classic electroshock. The cardiovascular system is strongly affected. During the initial high current level, the heart is usually irregular, but regularity returns promptly when the current level is reduced. During the treatment, the blood pressure rises (both systolic and diastolic) 50% to 100% above the original levels. This is not dangerous unless there is advanced arterio-sclerosis. One of our patients was a hypertensive individual who safely received 18 treatments. In one of these, his pressure readings were 230+/130 at 45 seconds of electro-narcosis, 280+/120 at

directly attributable to the treatment. One patient died by accident or purposely in a tub of scalding water, not on a treatment day.

THE NUMBER OF TREATMENTS varies from patient to patient. In our group, we have regarded 15 treatments as a minimum, and many have received over 30. A few have had 50 or more. Treatments are administered three times weekly for the first 3 or 4 weeks, then twice weekly until a good remission is obtained. During the latter part of this period, the treatment is usually given as an "ambulatory" procedure. It may be given on an ambulatory basis from the beginning to properly chosen patients. After the re-

mission is obtained, experience indicates that relapses will be minimal if "maintenance" treatments are continued once weekly over a long period, several months in some patients. This seems to allow the patients to resume normal environmental relationships and responsibilities safely, while consequent tensions are continuously dissipated through the treatment as long as they continue to develop. Their development gradually subsides under such technique in our experience.

Indications for the treatment are most clearly derived from the results obtained in various groups of patients. Only the patients under the author's control are considered in the tabulated results (Table 2).

**Results.** The results of treatment here reported are to be interpreted with the important consideration that almost all of these patients had been subjected to other forms of treatment, chiefly insulin and electroshock, alone or in combination. The patients, therefore, represent a group of treatment failures by previous standards. Among the private patients 29 of 41 are thought by strict criteria to be much improved or recovered, 10 improved to a less degree, and only 1, a schizophrenic of 20 years illness, unimproved. Of the 10 "improved", 6 are still hospitalized, 1 is employed, and 2 are active housewives and 1 is a retired clergyman, much better adjusted. With further attention the results in these should improve further. Follow-up periods are not sufficiently long to make the results conclusive but the rate of relapse within 6 months of completing treatment is not more than 2 in 15, and these are patients out of our control. The other patients are continuing to improve in their social and industrial adaptation in a manner which previous experience with other treatments indicates will continue to be productive and useful. The State Hospital patients present a different, but

essentially no less favorable aspect. They are all suffering from chronic illness, resistant to previous intense treatment. In some who are only moderately improved, the electro-narcosis has been the means of achieving for the first time a peaceful hospital situation. The potential benefit from treatment in these patients is often obstructed by difficult family situations and the adverse State Hospital surroundings. In spite of this, several outstanding cases present themselves as useful social individuals after long and apparently hopeless mental invalidism. Our continuing work with these people is developing, as far as conditions permit, in greater individualization of management and more prolonged treatment.

The most favorable diagnostic groups, according to the official classification, for application of electro-narcosis are the affective psychoses: the depressed manic depressive and melancholic involution psychoses; the paranoid psychoses in both schizophrenic and involution groups, including late developing paranoid conditions difficult to classify and sometimes called "paraphrenia"; and the catatonic reactions, both depressed and excited. In addition, a limited number of individuals with psychoneurotic reactions, chiefly evident in "compulsive" anxiety characterized by repetitious self-disparagement and self-accusation, religious scruples, and the like, have been treated. Apparently, if any one characteristic can be seen which runs through the entire group, it is the presence of deep anxiety, otherwise unapproachable by any means whatever. It is such anxiety which the electro-narcosis alleviates, in the author's opinion, as no other method, with the possible exception of lobotomy, can.

Brief case reports of a few neurotic individuals with "compulsive" anxiety and guilt relieved by this treatment will be of interest:

Case Reports: CASE 1. Rev. T., a clergyman who over a period of years became unable to carry on his work, celebrate mass, hear confessions, etc., experienced a total failure with Insulin. After electro-narcosis, he has resumed all of his duties, no longer feels contaminated or unworthy.

CASE 2. H. R., a man of 30, with chronic syphilophobia, was previously partly relieved by intensive psychotherapy and electroshock, but had a recurrence in much more severe form after 2 years with associated somatic symptoms, headache, dizziness, dyspepsia. He was relieved by electro-narcosis and returned to work and normal marital relationship.

CASE 3. T. J., a girl of 19, was totally disabled by a sense of guilt associated with religious scruples and obscene thoughts of characteristic "ruminative" variety. She failed to improve with electroshock, but was much improved by electro-narcosis, so that she could help with work at home, and go to church; only 8 treatments were given, which we considered inadequate, but we could not secure further cooperation from the family.

CASE 4. H. C., a man of 50 who had developed a ruminative anxiety about having sold a prosperous business, suffered from total sleeplessness and marked agitation. After treatment, he became a cheerful, energetic man; moved to California and bought a new business.

CASE 5. V. V., a woman of 28, was beset by religious scruples and feelings of sinfulness, unworthiness and contamination. After 20 treatments she was able to work as a cashier in a college cafeteria, have dates, enjoy social contacts and is able to see with some humor her remaining symptoms.

In our experience dangers of the treatment are minimal or non-existent.

As previously stated, there have been no skeletal complications. One patient suffered the loosening of a tooth. No cardio-vascular complications have occurred, even in the one patient with severe hypertension, and several with inactive rheumatic heart disease. We consider active organic disease of the brain (such as recent hemiplegias and untreated neurosyphilis), acute infections, recent cardiac lesions or failure, and severe renal deficiency as contraindications to this treatment. In 2 patients we have seen the delirium, called by some authors the "amnestic reaction", after a number of treatments. As in the same type of reaction occurring after ordinary electroshock treatment, the condition clears in a period of 7 to 21 days, without residual difficulty.

Summary. (1) The technique of electro-narcosis is described in detail.

(2) Very favorable results in private patients and moderately favorable results in State Hospital patients have been obtained after previous treatment failures by other measures.

(3) The treatment, in common with the more classical electroshock, is without appreciable danger.

(4) Anxiety, whether expressed as a psychotic reaction with depressive, paranoid or catatonic features, or as a neurosis, is the chief indication for the treatment.

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# STUDIES UPON THE RELATION BETWEEN PLASMA ANTITHROMBIN AND HEPARIN\*

## I. INFLUENCE OF PLASMA ANTITHROMBIN ON PROTHROMBIN TIME

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Kazal and Arnow<sup>9</sup> found that lyophilization of normal human plasma did not cause an appreciable loss of prothrombin, provided that marked alteration of the normal plasma pH was avoided. The "loss" reported by other investigators<sup>15</sup> appears to be an artefact produced by restoration of the plasma by distilled water or with improper solutions of carbonic acid. Kazal and Arnow found that the optimum pH for determination of plasma prothrombin values of lyophilized citrated human plasma, using Quick's method, was between 7.4 and 7.8, and that in this range the prothrombin values very closely approximated those of the original plasmas. Tocantins<sup>17</sup> found that a loss of prothrombin activity occurred when citrated or oxalated plasmas were exposed to an *air current*. A simultaneous increase in pH occurred. The prothrombin activity could be brought back to essentially normal by the treatment of the aereated plasma with CO<sub>2</sub>. Quick<sup>11</sup> repeated Tocantins's experiments and reported aereation of dog and rabbit plasma at 38°C. did not cause a loss of prothrombin activity.

Banfi, Tanturi and Bay<sup>2</sup> observed that a loss of prothrombin activity occurred gradually in *stored* human plasma after 4 or 5 days. This "loss" was to a certain extent only apparent and due to the formation of an antithrombin in *stored* plasma. The in-

fluence of this antithrombin on the prothrombin time of stored plasma was easily shown when *stored prothrombin-free plasma* was used as a diluent.

In the course of experiments undertaken to prepare a stock of lyophilized prothrombin-free plasma for use as a plasma diluent, we found an increase in the natural antithrombin activity when compared to the same plasma before lyophilization. This was demonstrated by determining the "thrombin time" of both samples.

The following experiments were undertaken in an attempt to study: a) the antithrombin activity of various plasmas, and b) the influence of this antithrombin activity on the determination of prothrombin time by using a one-stage method. Experiments were carried out on fresh normal plasma, aged normal and prothrombin-free plasmas, aereated normal and prothrombin-free plasmas and lyophilized normal and prothrombin-free plasmas of dogs.

**Material and Methods.** *Blood.* The blood used throughout these experiments was obtained from fasting unanesthetized mongrel dogs through femoral artery puncture. The blood was drawn into dry syringes, immediately transferred into 15 cc. graduated centrifuge tubes containing sodium oxalate solution in the proportion of 9:1, and then centrifuged for 10 minutes

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after which the plasma was pipetted into dry test tubes.

*Prothrombin determinations* were done by the one stage method of Quick<sup>12</sup> as modified by Tanturi and Banfi,<sup>16</sup> using a lyophilized thromboplastin prepared from acetone dried triturated rabbit brain. Thromboplastin so prepared was extremely stable.<sup>9</sup>

*Prothrombin-free plasma* was prepared by treating normal oxalated plasma with a 30% suspension of barium sulfate.<sup>16</sup> Washing of the sus-

thrombin solution was mixed with 0.2 cc. of oxalated dog plasma. In every experiment the dilution of hemostatic globulin with distilled water was freshly prepared and its strength tested against a control of a fresh sample of plasma.

*Procedures Employed in Treatment of Plasmas.* *Lyophilization* was accomplished after preliminary freezing in a mixture of methyl cellulose and crushed solid CO<sub>2</sub>. Reconstitution was achieved by the addition of neutral dis-

TABLE 1. THROMBIN TIMES OF DIFFERENT PLASMAS ASSAYED

Plasmas	Number of Experiments	Time in Seconds	
		Range	Average
Fresh.....	60	17-20	18.5
Fresh prothrombin-free...	68	17-20	18.5
Stored (16 days).....	18	20-30	25
Stored prothrombin-free (16 days) .	10	20-30	25
Stored (29 days).....	8	40-60	50
Aerated.....	5	50-60	55
Aerated prothrombin-free.....	4	50-60	55
Lyophilized.....	10	50-100	75
Lyophilized prothrombin-free.....	15	50-100	75

To 0.2 cc. of plasma were added 0.1 cc. of hemostatic globulin (Lederle) diluted in distilled water in proportion 1:20. All determinations were carried out in duplicate in test tubes 12 by 75 mm. at 37° C.

pension was carried out, using distilled water made neutral by the synthetic resin polyethylene polyamine methylene. This procedure made the suspension more stable. Repeated testing of the plasma so prepared failed to show any evidence of clotting or fibrin precipitates when mixed with the calcium-thromboplastin mixture and observed for as long as 18 hours at 37°C. The specific adsorbant character of barium sulfate for prothrombin has been confirmed by others.<sup>4,11</sup>

*Thrombin and "thrombin times":* Two different thrombins, both of which gave equivalent results, were used. One was prepared from human plasma using the procedure of Eagle;<sup>5</sup> the other was the so-called "hemostatic globulin" (Lederle). Both the human thrombin in dilution 1:10 and the "hemostatic globulin" in dilution 1:20 gave similar "normal" thrombin times of 17 to 20 seconds when 0.1 cc. of

tilled water to the original volume. The lyophilized plasmas were kept either in vacuo or stored in a dessicator over calcium chloride at room temperature (20°-25°C.).

*Stored plasmas:* These were kept covered in a refrigerator (5°C.).

*Aerated plasmas:* Procedures similar to those described by Tocantins<sup>17</sup> and Quick<sup>11</sup> were employed. In all these experiments care was taken to prevent bubbling and consequent surface denaturation. When CO<sub>2</sub> was blown over alkaline plasmas care was taken not to shift the pH beyond 7.

*Solutions and Reagents. Water:* In the early part of the study ordinary distilled water was used but later distilled water treated with the synthetic resin polyethylene polyamine methylene was used. The water so treated is neutral.

*Protamine* solutions were prepared by dissolving 100 mg. of protamine

sulfate (Lilly) in 100 cc. of distilled water. Such solutions showed a tendency to deteriorate and were frequently prepared. The pH of the fresh solution was 7.0. When deterioration occurred, the solution had a pH of 6.3 and had lost most of its activity.

*Sodium oxalate* solutions were prepared by dissolving 1.34 gr. sodium oxalate per 100 cc. distilled water.

times of a *normal sample* of plasma by diluting it with the variously treated plasmas can be seen. It is apparent that the lengthening of the prothrombin times parallels the anti-thrombin activity of the different plasmas used as diluents.

In Table 3 the influence of pH on the antithrombin activity of *aerated* or *lyophilized* plasmas when treated

TABLE 2. PROTHROMBIN TIMES OF FRESH PLASMA USING VARIOUS PLASMAS AS DILUENTS

Plasma Tested	Plasma Diluent	Prothrombin time (Dilution)			
		0	1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	12	17.6	23.3	33.6
Fresh normal	Aerated prothrombin-free	—	19	25	38
Fresh normal	Stored prothrombin-free	—	19.5	26	41
Fresh normal	Lyophilized prothrombin-free	—	24	32	60

Prothrombin times are averaged results of 14 determinations for each plasma diluent assayed.

TABLE 3. EFFECT OF CO<sub>2</sub> ON pH AND THROMBIN TIME

Plasmas	Before CO <sub>2</sub>		After CO <sub>2</sub>	
	Thrombin Time (Seconds)	pH	Thrombin Time (Seconds)	pH
Fresh	18	7.8	12	6.9
Fresh prothrombin-free	20	—	—	—
Aerated	30	8.1	16	7.0
Stored Prothrombin-free	43	8.2	18	7.4
Lyophilized	no clot in 2 min.	9.05	16	7.03
Lyophilized Prothrombin-free	no clot in 2 min.	9.0	15	7.0

To 0.2 cc. of plasma were added 0.1 cc. of hemostatic globulin (Lederle) diluted in distilled water in proportion of 1:20. All determinations were carried out in duplicate in test tubes 12 by 75 mm. at 37°C. Thrombin times are averaged results of 6 determinations for each plasma assayed. Ph determinations were done using a glass electrode potentiometer (Beckman). The source of CO<sub>2</sub> was crushed, dried ice. The current of CO<sub>2</sub> was passed through the plasma during a period of 5 to 10 seconds.

*Calcium chloride* solutions were 0.025 molar (0.28 gr. per 100 cc.) and *normal saline* solutions, 0.9%. All reactions were carried out in duplicate in test tubes 12 by 75 mm. at 37°C.; all measurements of volume with volumetric flasks, volumetric or serological pipettes (0.2 cc. graduated to 0.001 cc.); and time measurements with a stop watch graduated to 0.2 seconds. pH determinations were done using a glass electrode potentiometer.

**Results:** In Table 1 the "thrombin times" of the various plasmas are compared with those of fresh plasmas. In Table 2 the effect on the prothrombin

with CO<sub>2</sub> is shown. The different anti-thrombin activity found by us could be explained on the basis of differences of pH and accordingly the experiments recorded in Table 4 were done. In Table 5 the effect of CO<sub>2</sub> on the thrombin time and prothrombin time of *lyophilized plasmas* is recorded. It is shown that the loss of prothrombin activity of *lyophilized plasma* is only apparent and that the "loss" can be restored bringing the pH back to normal by treatment with CO<sub>2</sub>. An excessive amount of CO<sub>2</sub> will produce an acid plasma with a lengthened prothrombin time consequent to a decreased prothrombin level.

The variations of antithrombin activity and its direct influence on the prothrombin time of the plasma, although closely correlated with changes in pH, could also be interpreted as variations of activity of the "heparin complement" of these plasmas as affected by changes in pH. With this idea in mind, we studied the effect of protamine sulfate on the antithrombin activity of the different plasmas. In Table 6 the results of these experiments are recorded and it is apparent that protamine decreases the antithrombin activity of the plasmas studied.

bin as can be seen by the experiments recorded in Table 8. On the other hand, not only the different plasmas studied, but also the normal or fresh plasmas, varied widely in their antithrombin activity. Thus, the accurate adjustment of the quantity of protamine to be added to decrease the antithrombin activity without further decreasing prothrombin activity, or concentration, was difficult (Tables 6, 8, 12).

The influence of protamine was checked in regard to its effect on the pH of plasmas. In Table 9 this lack

TABLE 4. INFLUENCE OF pH ON THROMBIN TIME AND PROTHROMBIN TIME OF FRESH PLASMA USING DIFFERENT PLASMAS AS DILUENTS

#### THROMBIN TIME

Plasmas	Time (Seconds)	pH
Fresh	19	7.8
Fresh prothrombin-free	22	8.0
Stored prothrombin-free	43	8.2
Lyophilized prothrombin-free	no clot in 2 min.	9.09

#### PROTHROMBIN (Seconds)

Plasma Tested	Plasma Diluent	0	Dilution		
			1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	12	16	22	33
Fresh normal	Stored prothrombin-free	—	19.5	26	41
Fresh normal	Lyophilized prothrombin-free	—	19.7	31.1	50.5

To determine the effect on the prothrombin time of the reduction of the antithrombin activity by protamine, the following experiments were done, first using fresh prothrombin-free plasma and lyophilized prothrombin-free plasma as diluents of normal fresh plasma and then comparing the results of the prothrombin times so obtained with the prothrombin times of samples of the same fresh plasma similarly diluted with protamine treated lyophilized prothrombin-free plasma (Table 7). Many similar experiments were done, but these results were not constantly obtained, not because the plasmas varied regarding the interaction of protamine and antithrombin, but because an excess of protamine exerts a depressant effect on prothrom-

of change of pH is clearly shown and the decrease of antithrombin activity is notable. The reduced antithrombin activity is also reflected on the prothrombin times. In Table 10 similar experiments, which were carried out in an attempt to demonstrate the lasting effect of protamine on the pH and antithrombin of lyophilized plasma, are recorded.

We have also studied the effect of protamine on the antithrombin activity and pH of lyophilized human plasma and the results are recorded in Table 11.

In view of these results, the effect of the addition of increasing the amount of protamine on the antithrombin activity and prothrombin time of stored and fresh normal oxalated plasma was



studied, using samples of blood obtained from 3 dogs (Table 12). It is shown that fresh plasmas varied in their "normal" antithrombin activity, so undoubtedly the quantities of protamine added influenced the prothrombin activity and the fibrinogen. This is in contrast with the wider range observed when protamine is added to lyophilized or stored plasmas with high antithrombin activity.

**Comments:** The increase of antithrombin activity of plasma after 4 to 5 days' storage as found by Banfi, Tanturi and Bay has been confirmed. The increase of antithrombin activity is not related to the presence of prothrom-

thrombinemia to the alkalinity of lyophilized plasma due to the lack of  $\text{CO}_2$ . We have confirmed the results of Kazal and Arnow in regard to the effect of  $\text{CO}_2$  in bringing the prothrombin time of lyophilized plasma of dogs back to normal, but we regard the changes observed in prothrombin times as being more closely related to the enhanced antithrombin activity brought about by the process of lyophilization. This antithrombin activity is reflected on the prothrombin times of the lyophilized plasmas as well as on the normal fresh plasmas when prothrombin determinations of the latter are carried out using lyophilized pro-

TABLE 5. EFFECT OF  $\text{CO}_2$  ON THROMBIN TIME AND PROTHROMBIN TIME OF LYOPHILIZED PLASMA

THROMBIN TIME					
Plasma	Before CO <sub>2</sub> Time (Sec.)	pH		After CO <sub>2</sub> Time (Sec.)	pH
Lyophilized	no clot in 2 min.	9.05		16	—
Lyophilized prothrombin-free	no clot in 2 min.	8.9		18	7.03
PROTHROMBIN TIME (SECONDS)					
Plasma Tested	Plasma Diluent	0	1/10	1/20	1/50
Lyophilized	Lyophilized prothrombin-free treated with CO <sub>2</sub>	19	17	23	36
Lyophilized treated with CO <sub>2</sub>	ID	13	15	20	30
Lyophilized After Repeated Treatment With CO <sub>2</sub> *	ID	18	23	31	46

\* This plasma after repeated treatment with  $\text{CO}_2$  (pH 6.3) decreased its prothrombin. As it is known excess of  $\text{CO}_2$  decreases prothrombin.

bin in stored plasma because similar increases of antithrombin activity occur in stored prothrombin-free plasma, lyophilized normal and prothrombin-free plasma and aereated normal and prothrombin-free plasma. That stored, aereated and lyophilized plasmas have prolonged prothrombin times has also been confirmed.

The decrease of prothrombin found by some investigators in aereated, stored and lyophilized plasmas is to some extent only apparent. In the case of lyophilized plasma, Kazal and Arnow attributed the apparent hypopro-

thrombin-free plasma as diluent. The fact that the lyophilized prothrombin-free plasmas also show an increase of the antithrombin activity points out that, to a considerable extent, the decrease of prothrombin observed by other investigators in similar conditions is due to an increased antithrombin activity in the clotting system studied.

The increased antithrombin activity of aereated and stored plasmas is also reflected in the prothrombin times of these plasmas and on normal plasmas in which the determinations of pro-

thrombin were carried out using aereated or stored prothrombin-free plasmas as diluents.

The increased antithrombin activity observed apparently exerts its effect on the second stage of coagulation which, in the one-stage methods of prothrombin determinations, appears to be an important factor in the resulting prothrombin time. It is generally agreed that the one-stage methods of prothrombin determination measure a clotting time which is theoretically the summation of the time corresponding to the conversion of prothrombin to thrombin (1st stage), and that of the

the one-stage methods of prothrombin determination are used to test *normal* plasmas, the influence of the antithrombin activity is overcome by the excess of thrombin which results from the addition of an excess of thromboplastin.

The results of our experiments on different plasmas with enhanced antithrombin activity emphasize the importance of the very frequently neglected factor of the variation of the anti-thrombin activity, and the equally neglected factor of the pH of the reagents in the clotting system under study.

TABLE 6. EFFECT OF PROTAMINE SULFATE ON ANTITHROMBIN OF DIFFERENT PLASMAS

Plasmas	Thrombin Time (Seconds)	
	Before Protamine	After Protamine
1. Fresh normal	18	13.5
2. Fresh prothrombin-free	17	15.8
3. Stored (5 days)	30	20
4. Stored prothrombin-free (5 days)	30	14
5. Aereated	60	18
6. Lyophilized prothrombin-free	173	50

All samples received 0.3 mg. of protamine sulfate per cc. of plasma. Samples 5 and 6 received 0.65 mg. and 1 mg. of protamine sulfate per cc. of plasma respectively.

conversion of fibrinogen to fibrin by the action of the thrombin already formed (2nd stage). It is easy to understand then that not only a decrease in the rate of conversion of prothrombin, concentration or any other interference in the first stage of the clotting mechanism will give a prolonged prothrombin time but any interference in the second stage will produce similar results. A good example of the second possibility is that of the presence of heparin in excessive amounts, such as is observed in the plasmas of anaphylactic or peptone-shocked animals, or in the plasmas of patients who have received intravenous injections of heparin to prevent thrombosis. In both cases, a definite prolongation of prothrombin time which is not due to a corresponding decrease of prothrombin concentration is observed.<sup>3</sup> When

By treatment with CO<sub>2</sub> the antithrombin activity of the plasmas studied by us was brought back to "normal." Hence, the prothrombin times also became "normal," possibly through restoration of the pH optimal for coagulation. The demonstration that protamine sulfate does not change the pH, but does change the antithrombin effect, which is also reflected by the shortened prothrombin times, adds support to the belief that these changes are not solely due to changes in pH.

From the results of some of the experiments reported here, it can be said that protamine exerts a depressant effect on prothrombin. Some combination of protamine with prothrombin which would interfere with the conversion of prothrombin to thrombin might be the explanation. It has been shown<sup>12</sup> that when protamine and hep-

arin are present in proportions other than 3:1, which is the proportion found between heparin and protamine dosage in *in vitro* studies, then the substance in excess lengthens the clotting time. That this lengthening is not due to any interference in the 2nd stage of clotting is shown by the shortening of thrombin times obtained when prota-

ing the 5 minute period of treatment prior to centrifugation. In any event, the clots we obtained were firm and similar to normal clots. Furthermore, any lack or decrease of fibrinogen would be reflected by a lengthening of the thrombin times.

As we have shown, protamine not only decreases the enhanced antithrom

TABLE 7. PROTHROMBIN TIME OF FRESH PLASMA USING LYOPHILIZED PROTHROMBIN-FREE PLASMA TREATED WITH PROTAMINE

Plasmas		Thrombin Time (Seconds)			
Fresh		20			
Fresh prothrombin-free		20			
Lyophilized prothrombin-free		116			
Lyophilized prothrombin-free + protamine		36			

PROTHROMBIN TIME (SECONDS)					
Plasma Tested	Plasma Diluent	0	Dilution		
			1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	12	18	22	30
Fresh normal	Lyophilized prothrombin-free	—	21	29	34
Fresh normal	Lyophilized prothrombin-free treated with protamine*	—	18	23	31.4

\* To 3.5 cc. of chilled (8° C.) plasma 1.2 mg. of protamine sulfate was added. After 5 minutes at 8° C., the plasma was centrifuged.

TABLE 8. EFFECT OF PROTAMINE SULFATE ON THROMBIN TIME AND PROTHROMBIN TIME OF FRESH PLASMA

Plasmas		Thrombin Time (Seconds)			
Fresh normal		20			
Fresh prothrombin-free		19			
Fresh normal + protamine (0.3 mg. 1 cc.)		15			
Fresh prothrombin-free + protamine (0.3 mg. 1 cc.)		16			

PROTHROMBIN TIME (SECONDS)					
Plasma Tested	Plasma Diluent	0	Dilution		
			1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	13	18	23	33
Fresh normal + protamine	Fresh prothrombin-free + protamine	18	31	35	48*

\* pH of lyophilized prothrombin-free + protamine at the end of experiment 8.7.

mine is added to normal plasmas. Mylon, Winternitz and Suto-Nagy<sup>10</sup> found that the addition of protamine to plasma leads to a rapid and extensive precipitation of fibrinogen. The temperature after addition of protamine influenced this precipitation. We believe that we have avoided extensive precipitation of fibrinogen by chilling the plasmas and by keeping their temperature between 5° and 8°C., dur-

bin activity of lyophilized or stored plasmas, but also decreases the activity of the antithrombin of fresh plasmas. The similarity of action of protamine on heparin, protamine action on "normal" antithrombin activity and on the enhanced antithrombin activity of the plasmas studied lead to the belief that the differences in antithrombin activity observed in the plasmas studied is due to different quantities

of heparin present in them. We have found an approximate proportion between protamine and the antithrombin activity of normal plasma. A dose of 0.3 mg. to 0.4 mg. of protamine per cc. of plasma of dogs reduced the thrombin times of normal plasmas to an extent which cannot be further reduced no matter how much protamine is added. One mg. to 1.50 mg. of protamine per cc. of plasma pro-

activity of lyophilized or stored plasma. In the latter cases a greater quantity of protamine is necessary to bring the antithrombin activity back to normal.

The so-called normal antithrombin of plasma has been identified by Quick<sup>13</sup> as present in the albumin fraction but not in crystalline serum albumin as shown by Jaques and Mustard<sup>8</sup> and by Ziff and Chargaff<sup>18</sup>. As is

TABLE 9. EFFECT OF PROTAMINE SULFATE ON THE ANTITHROMBIN AND pH OF PLASMA

Plasmas	Thrombin Time (Seconds)	pH
Fresh normal	20.2	7.8
Fresh prothrombin-free	20.5	7.9
Lyophilized prothrombin-free	116	8.9
Lyophilized prothrombin-free + protamine	30	8.7

#### PROTHROMBIN TIME (SECONDS)

Plasma Tested	Plasma Diluent	Dilution			
		0	1/10	1/20	1/30
Fresh normal	Fresh prothrombin-free	12.9	16	22	31
Fresh normal	Lyophilized prothrombin-free		21	29.5	45
Fresh normal	Lyophilized prothrombin-free treated with protamine*		17.7	22.2	31.4

\* pH of lyophilized prothrombin-free + protamine at the end of experiment, 8.7.

TABLE 10. DEMONSTRATION OF THE LASTING EFFECT OF PROTAMINE SULFATE ON pH AND ANTITHROMBIN OF LYOPHILIZED PLASMA

Plasmas	Thrombin Time (Seconds)	pH
Lyophilized prothrombin-free	no clot in 3 minutes	9
Lyophilized prothrombin-free + protamine	30	8.9
Lyophilized prothrombin-free + protamine and centrifuged	32	
After 35 mins. standing at room temp.	35	
After 65 mins. standing at room temp.	40	8.8
Uncentrifuged	30	
After 35 minutes standing at room temp.	36	
After 65 minutes standing at room temp.	42	8.8
Protamine sulfate	—	7.0
Thrombin solution	—	6.3

duced a precipitation of fibrinogen which interferes notably with the reaction. As has been said above, a slight excess of protamine also influences the prothrombin activity in clotting systems in which this substance has been studied. The proportion between protamine and antithrombin activity of normal plasma is in contrast with the proportion between protamine and antithrombin

well known, heparin acts only in the presence of this plasma fraction. According to Ziff and Chargaff the rate of clotting in a system containing thrombin, fibrinogen and heparin may depend entirely on the concentration of the heparin complement or normal antithrombin of that system. The same authors point out that the concentration of this complement in the blood may be the determining factor

to the individual response to heparin. Astrup and Darling<sup>1</sup> found that the so-called normal antithrombin is not identical to the antithrombin substance formed from heparin. This last compound, called by them "thrombin inhibitor," inactivates thrombin more rapidly than the normal antithrombin.

The loss of CO<sub>2</sub> which is a common factor in the plasmas studied seems to be closely related to the behavior of the antithrombin activity. The close relationship between pH and anti-

pound is inactive provided that it is stable at the pH of the assay. Jaques and Mustard<sup>3</sup> have obtained results similar to those of Fisher and state that if the reaction of heparin with the normal antithrombin of plasmas is similar to that of heparin with other proteins, it is probable that the isoelectric point of the normal antithrombin is more alkaline than the pH of plasma.

Our experiments show that the normal antithrombin activity of plasma in-

TABLE 11. EFFECT OF PROTAMINE ON ANTITHROMBIN AND pH OF LYOPHILIZED CITRATED NORMAL HUMAN PLASMA

Lyophilized plasma*	Thrombin Time (Seconds)	pH
Sample I	25	7.4
2 cc. of Sample I + 0.6 mg. protamine sulfate	14.6	7.4
Sample I (28 days old)	35	
2 cc. of Sample I (28 days old) + 0.6 mg. protamine sul.	25	
To the same sample was again added 0.6 mg. of pro. sul.	18	7.4

\* Standard Navy and Army package (Parke Davis and Co.). After made up, the solution was kept in the refrigerator (5° C.).

EFFECT OF CO<sub>2</sub> AND PROTAMINE ON ANTITHROMBIN, PROTHROMBIN TIME, AND pH OF LYOPHILIZED CITRATED NORMAL HUMAN PLASMA

Plasma Date	BEFORE CO <sub>2</sub>			Vol- ume (ML)	Time of CO <sub>2</sub> Pass- ing Through (Sec.)	AFTER CO <sub>2</sub>		
	Thrombin Time (Sec.)	Pro- thrombin Time (Sec.)	pH			Thrombin Time (Sec.)	Pro- thrombin Time (Sec.)	pH
Sample II (4-VI)	70	66	9.27	2	3	27	45	7.6
				2	5	27	43	7.3
				2	10	24	49	6.9
				2	15	28	52	6.9
				2	25	20	85	6.5

Plasma*	Thrombin Time	pH
Sample I (1-VI) 2cc. of Sample I + 3 mg. protamine	55	8.9
Sample II (4-VI)	20	8.8
2 cc. of Sample II + 3 mg. Pro.	70	9.2
	28	9.2

\* Standard Navy and Army package (Sharp & Dohne). This plasma was made up by adding 250 cc. of distilled water and kept in a refrigerator. Note the different quantities of protamine necessary to bring thrombin time back to "normal." Thrombin time and pH of a sample control normal fresh human oxalated plasma = 25 seconds and 7.5 respectively.

thrombin activity of plasmas points out that the antithrombin varies in activity according to the pH of the plasma. Fisher<sup>2</sup> found that while heparin combines with a large number of proteins under suitable conditions, the resulting heparin protein com-

creases with its alkalinity. However, the mechanism by which protamine inhibits the normal antithrombin activity of plasma is not easily understood.

Considering the basic character of protamine one possibility worthy of consideration is that the antithrombin

activity of normal plasma is due to the presence of heparin bound to the cofactor. The compound displays a relatively slight activity on the normal pH of plasma. Protamine neutralizes heparin, and hence reduces the antithrombin activity without changing the pH of plasma. Opposite changes which shift the pH of plasma to the alkaline side will establish appropriate conditions which enhance the activity

tivity as compared with the corresponding fresh plasma. The antithrombin activity was studied using a thrombin solution of constant activity.

2. The increased antithrombin activity is not related to the presence of prothrombin because the same changes occur in lyophilized, aged and aereated prothrombin free plasmas.

3. The effect of the increased antithrombin activity is reflected in the

TABLE 12. EFFECT OF PROTAMINE SULFATE ON THE "NORMAL" ANTITHROMBIN ACTIVITY PROTHROMBIN TIME OF STORED AND FRESH PLASMAS OF SEVERAL DOGS

Dog No.	Tube No.	Volume (cc.)	Appearance	Protamine (Mg.)	Thrombin Time (Sec.)	Prothrombin Time (Sec.)
1	1	2	clear	—	16.8	12.6
	2	2	clear	0.05	15.	15.1
	3	2	clear	0.1	16	16
	4	1.45	clear	.15	14.5	17.4
	5	1.41	clear	0.20	15.8	16
	6	1.0	clear	0.25	12.6	20
	7	1.02	clear	0.30	12.9	19
2	1	2.0	clear	—	25	13
	2	2.0	clear	0.4	15.5	17.5
	3	2.0	clear	0.5	16.	18
	4	1.44	cloudy	0.9	13.8	21
	5	1.45	cloudy	1.0	11.6	20
Tubes 4 and 5 centrifuged and the determinations repeated						
	4		clear		15	16
	5		clear		13	15
3	1	2	clear	—	16	13
	2	2	clear	0.4	14	17.5
	3	2	clear	0.5	13	20
	4	1.44	clear	0.2	13	19
	5	1.45	clear	0.4	12	20.5
stored plasma	1	2	clear	—	21.5	15.4
	2	2	clear	0.4	16.4	21
	3	2	clear	0.5	15.8	22
4	4	1.44	clear	0.2	16	20.6
	5	1.45	clear	0.4	14	22.4

of the compound heparin-cofactor and so increase the antithrombin activity of plasma. The protein, or factor to which heparin is bound, would not necessarily have any antithrombin activity per se. Further studies are required to clarify the hypothesis advanced.

Conclusion and Summary. 1. Lyophilized, aereated and aged plasmas show an increase of antithrombin ac-

prothrombin times of these plasmas and on the prothrombin times of fresh plasmas when plasmas with increased antithrombin activity are used as diluents.

4. The increased antithrombin activity may be brought back to normal by means of various treatments (CO<sub>2</sub>, protamine).

5. The antithrombin activity varies directly as the pH of plasma. How-

ever, protamine sulfate decreases the antithrombin activity without changing the pH of the plasma. It may be concluded that the decrease of prothrombin noted by other investigators in similar plasmas is due to the presence of the antithrombin and not solely due to changes of the pH.

6. Protamine sulfate has a tendency to decrease prothrombin and precipitate fibrinogen depending upon the quantity present.

7. With appropriate quantities of protamine sulfate the antithrombin

activity of fresh oxalated normal plasma can be reduced to a certain extent but no more, irrespective of the amount of protamine used. An approximate proportion between the quantity of protamine necessary to return to normal the thrombin times of certain plasmas and to reduce the antithrombin activity of normal plasmas has been demonstrated.

8. A hypothesis which suggests that heparin is the normal anticoagulant of plasma is presented.

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# EFFECT OF STREPTOMYCIN ON BLOOD CLOTTING TIME AND PROTHROMBIN TIME IN MAN\*

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RECENTLY, Macht<sup>6</sup> reported that streptomycin when administered parenterally shortened the coagulation time in rabbits and cats. Farrington and his co-workers,<sup>3</sup> investigating streptomycin toxicity in man, performed occasional determinations of the blood clotting and prothrombin times, but found them to be normal. Since streptomycin is one of the important antibiotics in clinical use at present, it would seem desirable to determine the influence it may have on the clotting mechanism in man.

TABLE 1.—PERTINENT CLINICAL DATA  
IN STREPTOMYCIN AND CONTROL  
GROUPS OF PHTHISIC PATIENTS

	Streptomycin Group (No. of Cases)	Control Group (No. of Cases)
Total No. of Patients	21	21
Age (range in years)	19-57	21-57
Activity of Lesion*:		
Class 1	14	15
Class 2	7	6
Collapse Treatment:		
Thoracoplasty	4	4
Pneumothorax	3	1
Pneumoperitoneum	1	0
Lobectomy	1	0

\* Clinical classification adapted from criteria of National Tuberculosis Association.<sup>1</sup>

**MATERIAL.** The patients selected for this study were 35 cases of pulmonary tuberculosis, 24 having far-advanced, 8 moderately advanced, and 3 minimal lesions. Of the 35 cases, 14 were receiving streptomycin in accordance with the protocol of the streptomycin research program of the Veterans' Administration, at the time this investigation was initiated. The remaining 21 were suitable controls. Seven of these were subsequently treated with streptomycin and retested as

part of the streptomycin group. Thus the treated and control categories each comprised 21 cases, 7 patients being common to both. The pertinent clinical data for both groups are listed in Table 1. They were matched as carefully as was clinically feasible in all essential respects. Particular pains were taken to assure close comparability in respect to clinical activity, for it has been claimed<sup>2,11,12</sup> that the level of prothrombin in phthisis is related principally to the severity of the disease. To facilitate this, the patients were classified into two broad categories, adapted from the criteria of the National Tuberculosis Association<sup>1</sup>: Class 1: Activity none or slight; Class 2: Activity moderate or severe.

**METHODS.** Two methods of investigation were employed: (a) Performance of repeated tests (3 to 5) at about the same time (from 1 to 2 hours following the morning dose of streptomycin) on different days over a period of several weeks. (b) Performance of tests serially, prior to and at 15, 30 and 90 minutes following the injection of streptomycin (or a control injection of distilled water).

Each patient in the streptomycin group received 0.5 gm. of streptomycin in 2 cc. of distilled water at 8:00 a. m. and 8:00 p. m. daily for 120 days by the intramuscular route. The average dose of streptomycin was 7.56 mg. per kg. per injection. The control patients were given 2 cc. of distilled water intramuscularly only during the performance of the serial tests.

All patients, otherwise, received substantially the same routine treatment of bed rest and symptomatic remedies as required.

Streptomycin blood levels were determined every 2 weeks by microbiological assay.<sup>9</sup> Blood for these estimations was usually obtained from 1½ to 2 hours after the morning dose. The average blood level for the group was 10 micrograms per cc. with a range of 5 to 40 micrograms. Streptomycin estimations could not be performed concomitantly with the serial tests, so that the actual levels at the time serial samples were taken is unknown.

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# ELSON: BLOOD CLOTTING TIME AND PROTHROMBIN TIME IN MAN

The presence of severe liver damage which might interfere with the response to streptomycin was sought for in all patients. None had clinical evidence of liver damage. Three streptomycin patients and 2 controls were found to have 3 plus cephalin flocculation reactions. However, a positive cephalin flocculation test alone was not regarded as significant of liver dysfunction unless confirmed by abnormal bromsulfalein retention; that is, more than 10% in 45 minutes, using 5 mg. per kg.

Blood was withdrawn with stasis from an antecubital vein by means of a 20 gauge needle into a syringe previously coated with mineral oil. Frothing was prevented by avoiding suction. If the vein was not entered on the first attempt, the needle was changed and another vein selected for puncture. The portion of blood withdrawn last was used for the Lee-White test. The rest of the blood was mixed with 1/10 volume of 0.1 M sodium oxalate in a conical tube, centrifuged at 2,000 r.p.m. for 10 minutes, and the supernatant plasma used for determination of the prothrombin time.

**Blood Coagulation Time:** The following modification of the Lee-White method was used: 1 cc. of blood was transferred, after removing the needle from the syringe, to each of two 10 by 75 mm. test tubes, which were placed at once in a water bath, maintained at  $37.5 \pm 2^\circ\text{C}$ . After standing 3 minutes the tubes were tilted simultaneously and gently to a uniform angle of  $90^\circ$  at  $\frac{1}{2}$  minute intervals. The end point was assumed to have been reached when the tubes could be held in an inverted position for 15 seconds without disrupting the clot. The interval from the entry of the blood into the syringe to the end point was recorded as the clotting time for each tube, and the results averaged to the nearest  $\frac{1}{4}$  of a minute. The error of this method was approximately 10%.

**Prothrombin Time:** The technique employed was a combination of modifications of the original Quick procedure.<sup>10</sup> All estimations were done in duplicate (and, when deemed advisable, in triplicate or quadruplicate) on a 5% dilution of the plasma sample.

The diluent used was a portion of the patient's own plasma rendered prothrombin-free with a 30% suspension of barium sulfate (barium plasma), according to the technique of Tanturi and Banfi.<sup>13</sup> A commercial thromboplastin (Difeo) was used in preparation of thromboplastin emulsion which was frozen and stored as suggested by Fuller.<sup>5</sup> The emulsion was prepared in bulk by suspending contents of 200 ampules (30 gml. in 500 cc. of oxalated saline, incubating at  $50^\circ\text{C}$ ., for 15 minutes with only occasional agitation; and separation of the coarser parti-

cles by filtration through cotton and gauze. The filtrate was apportioned in 1 to 3 cc. amounts in small test tubes, which were then stoppered and frozen.

Shortly before use, a tube of the frozen extract was removed, thawed at  $37.5^\circ$  in the water bath, and mixed with an equal volume of 0.02 M calcium chloride. After having reached the temperature of the water bath, 0.2 cc. of this mixture was blown from a micropipette into a 10 by 75 mm. tube containing 0.1 cc. of the 5% plasma, also at  $37.5^\circ\text{C}$ . The end point was distinct and easily detected by lifting the adherent clot out of the solution with a small nichrome wire loop.

**STATISTICAL ANALYSIS.** All mean differences obtained from the data were subjected to statistical computation by the methods of Fisher.<sup>4</sup> Differences are considered "significant" when the probability is less than 5 in 100 that chance would account for the result. When the critical ratio (CR) exceeds the 't' value obtained from the Fisher 't' tables, the difference is significant.

TABLE 2.—BLOOD CLOTTING TIMES AND BLOOD PROTHROMBIN TIMES IN NORMAL AND TUBERCULOUS PATIENTS

	A. Blood Clotting Times		Tuberculosis
	Normal		
No. of Cases	26	20	
Mean (Minutes)	7.75*	8.00*	
Standard Deviation	1.4	0.95	
* Statistical Analysis of Difference of Means			
t (from Fisher 't' table) = 2.00			
Critical Ratio (CR) = 0.69 (not significant)			
	B. Blood Prothrombin Times		Tuberculosis
	Normal		
No. of Cases	16	11	
Mean (Seconds)	35.2	35.2	
Standard Deviation	2.6	3.1	

**Results. Blood Clotting and Prothrombin Times of Normals and of Tuberculous Controls.** The results are summarized in Tables 2 A & B. These findings are in agreement with the few reports quoted by Muller<sup>7</sup> that the blood clotting time is unaffected in tuberculosis. The mean prothrombin time of 5% plasma in the normal and tubercular groups was identical. This series is too small to permit generalizations but tends to support the view of Poulsen and Plum<sup>8</sup> that phthisis has no appreciable effect on the prothrombin time. Analysis of our data revealed no correlation of the clotting

time or prothrombin time with age, activity or extent of the lesion in either the control or streptomycin group.

*Serial Clotting Times.* The means of the blood clotting times obtained serially and their standard deviations are recorded in Table 3. The significance of the mean differences between the various test periods is revealed by the statistical analyses of Table 4.

increase of one minute in the 90 minute period after streptomycin as well as increases between the 15 and 45, and 15 and 90 minute periods. This may, with equal justification, be interpreted as indicating a decline in coagulability. It is, of course, conceivable that streptomycin may be responsible for both effects, but when one turns to the control group (B), it is observed that

TABLE 3.—SERIAL MEAN BLOOD CLOTTING TIMES (IN MINUTES) OF CONTROL GROUP AND TUBERCULOUS PATIENTS INJECTED WITH STREPTOMYCIN

13 Streptomycin Patients					13 Control Patients				
Minutes after Streptomycin					Minutes after Distilled Water				
Before Injection	15	45	90		Before Injection	15	45	90	
7.75	6.75	8.5	8.75		7.5	7.5	8.0	7.0	
Standard Deviation	0.99	0.84	1.62	1.06	Standard Deviation	1.03	1.36	1.12	0.83

TABLE 4.—STATISTICAL ANALYSIS OF MEAN DIFFERENCES OF SERIAL BLOOD CLOTTING TIMES

A. Within Streptomycin Group				
Intervals Being Compared	Diff. of Means* in Minutes	SD**	CR***	t****
Before — 15' after	-1.00	0.36	2.77	2.056
Before — 45' after	+0.75	1.78	0.42	2.056
Before — 90' after	+1.00	0.40	2.56	2.056
15' — 45' after	+1.75	0.50	3.50	2.056
15' — 90' after	+2.00	0.38	5.29	2.056
45' — 90' after	+0.25	0.53	0.47	2.056
B. Within Control Group				
	0.0	0.48	0.0	2.056
Before — 45' after	+0.5	0.42	1.19	2.056
Before — 90' after	-0.5	0.37	1.36	2.056
15' — 45' after	+0.5	0.55	0.92	2.056
15' — 90' after	-0.5	0.45	1.11	2.056
45' — 90' after	-1.0	0.39	2.56	2.056
C. Between Control and Streptomycin Groups				
Before Injections	+0.25	0.39	0.64	2.056
15' after	-0.75	0.45	1.67	2.056
45' after	+0.50	0.54	0.93	2.056
90' after	+1.75	0.38	4.60	2.056

\* In A & B plus sign (+) indicates increase from period before to period after, minus sign (-) indicates decrease; in C, plus sign (+) indicates increase in streptomycin, over control group; the minus sign (-) the reverse.

\*\* SD=Standard Error of Difference

\*\*\* CR=Critical Ratio; bold-face figures are significant.

\*\*\*\* t=Obtained from Fisher 't' table.<sup>4</sup>

It will be noted that there is a significant decrease in the 15 minute period. From this it might appear that there is an increase in coagulability after streptomycin. However, it will be noted that there is also a significant

there is a significant decrease in clotting time from the 45 minute to the 90 minute period. Since streptomycin obviously cannot be responsible for this decrease in the control group, it would be unwarranted to hold it ac-

countable for the similar change in the streptomycin group.

On the other hand, one cannot entirely exclude the possibility that streptomycin may cause the increase noted in the 90 minute period, particularly, since no such significant increase is found in the control group. Moreover, there is a rather significant increase of

limited amount of data, as well as the possible existence of other unknown factors which may influence them, makes it necessary, that any differences found within the streptomycin group, or between the streptomycin and control groups, significant though they be statistically, be consistent and unequivocal before attributing them to strep-

TABLE 5.—SERIAL MEAN PROTHROMBIN TIMES\* OF CONTROL GROUP AND OF TUBERCULOUS PATIENTS INJECTED WITH STREPTOMYCIN

13 Streptomycin Patients					13 Control Patients				
		Minutes after Streptomycin					Minutes after Distilled Water		
Before Injection		15	45	90	Before Injection		15	45	90
		42.7	42.8	42.7	41.5	42.4	40.5	41.9	
Standard Deviation	2.96	3.30	3.14	3.20	5.63	4.93	3.68	5.93	

\* of 5% plasma in seconds

1.75 minutes (CR equals 4.60) when comparison is made between the 90 minute periods of the control and streptomycin group (Table 4 C). However, there are no significant increases, when the 15 minute and 45 minute periods of both groups are compared. Thus, the meaning of the isolated increase in the 90 minute period of the streptomycin, over the control group becomes problematical.

*Serial Prothrombin Times.* The means of the prothrombin time for the separate test periods and their standard deviations are presented in Table 5. Statistical analysis of the mean differences reveals no significant differences within or between the 2 groups.

*Blood Clotting Times and Prothrombin Times Obtained on Different Days.* The composite results are shown in Tables 6 and 7. No significant differences can be demonstrated between the mean prothrombin times or the mean clotting times of the streptomycin and control groups.

*Discussion.* Although serial blood clotting times following streptomycin show some significant differences, these are too indeterminate to ascribe them unconditionally to its action. The

tomycin rather than to some other unknown variable. However, while not conclusive, the data (Table 4) suggest that streptomycin exerts an anticoagulant effect.

From the blood clotting times obtained on different days no effect of streptomycin is discernible. It should be emphasized that the comparisons made by this method of study are of grosser nature. Averages obtained for 2 hour periods are being compared. Differences may occur within this period which are obliterated by the process of averaging. Hence, the failure to detect any effect by this method does not necessarily imply that the differences noted in the serial study cannot be attributed to the action of the antibiotic.

The results of the prothrombin time studies both serially and on different days indicate that streptomycin exerts no demonstrable effect on the prothrombin time.

Macht's<sup>6</sup> demonstration of the decided thromboplastic action of streptomycin in rabbits and cats was not duplicated in these studies in man. The lack of effect cannot be attributed to insufficient dosage. Macht employed

total dosages ranging from 1 to a maximum of 5 mg. per animal, a level not likely to exceed the average injected dose 7.56 mg. per kg. used in our patients. Differences of species or of technique may, of course, be responsible.

Another possibility which cannot be adequately eliminated is that the tuberculous process itself may have masked or interfered with the response

Lee-White and Quick techniques. A parallel series of 21 phthisic patients served as controls. Two methods of investigation were used: (a) tests during the same hours on different days; (b) serial tests during a 90 minute period immediately after the injection of streptomycin.

2. No correlation between the age, activity, or extent of the tuberculosis, and the clotting or prothrombin times

TABLE 6.—COMPARISON OF MEAN BLOOD CLOTTING TIMES OF STREPTOMYCIN PATIENTS AND OF CONTROLS, PERFORMED ON DIFFERENT DAYS

14 Streptomycin Patients		11 Control Patients	
	Mean Clotting Times in Minutes		Mean Clotting Times in Minutes
	8.75°		8.5°
Standard Deviation	1.26	Standard Deviation	0.3

° Statistical analysis of Difference of Means:  $t$  (from Fisher 't' table)=2.06; CR=0.54 (not significant)

TABLE 7.—COMPARISON OF MEAN PROTHROMBIN TIMES OF STREPTOMYCIN PATIENTS AND OF CONTROLS, PERFORMED ON DIFFERENT DAYS

14 Streptomycin Patients		12 Control Patients	
	Mean Prothrombin Time in Seconds		Mean Prothrombin Time in Seconds
	36.1°		37.5°
Standard Deviation	2.87	Standard Deviation	3.7

° Statistical analysis of Difference of Means:  $t$  (from Fisher 't' table)=2.05; CR=1.08 (not significant).

to streptomycin. A thorough search of the literature yields no positive information on this point. On clinical grounds, it is quite improbable that such is the case. The essentially normal levels of blood clotting and prothrombin activity found in our patients, as well as by others,<sup>7,8</sup> would seem to indicate that the physiological mechanisms involved in regulating these functions are normal in tuberculosis, and hence can be expected to respond normally to the action of coagulant or anticoagulant agents. It would be necessary, however, to restudy the effects of streptomycin in normal, healthy individuals to be certain that tuberculosis does not affect the response.

**Summary and Conclusion.** 1. The effects of streptomycin on the blood clotting and prothrombin times of 21 patients with pulmonary tuberculosis were studied by modifications of the

was found in either the control or streptomycin groups.

3. No significant effects upon the prothrombin time could be demonstrated by either method of investigation.

4. Significant differences between the mean clotting times of some of the test periods were obtained by the serial method, but the results were inconclusive and could not be ascribed with certainty to the influence of streptomycin. No significant differences were detected between the mean clotting times of the streptomycin and control group by the "different day" method of study.

5. Although there are no clinical grounds for believing that tuberculosis would affect the behavior of the clotting and prothrombin times in response to streptomycin, this possibility cannot be excluded in this study.

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# THE CONTROL OF DICUMAROL THERAPY\*

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With the increasing use of dicumarol in the prophylactic and active treatment of thrombo-embolic conditions, the control of its administration and effects becomes increasingly important.

According to the present concept the chief effect of the drug is the depression of the plasma prothrombin, and on this basis a diminution in the clotting tendency of the blood. Several investigators<sup>5,19,28</sup> have found that the adhesiveness of the platelets is less in dicumarolized blood than in normal controls, suggesting a second factor by which the drug may produce an anti-clotting effect. The chief effort in the control of the administration of the drug, however, has been directed towards the maintenance of the plasma prothrombin at a level at which intravascular clotting will not occur and yet bleeding is not induced. In order to achieve this most workers in the field have employed the "one-stage" prothrombin determination described by Quick<sup>14</sup> or various modifications of it.

By diluting normal plasma to various concentrations, Quick set up percentage values of prothrombin corresponding to the clotting times of the various dilutions. Because of variations in the activity of thromboplastin solutions prepared in various laboratories, this percentage scale could not be used by all investigators, and rather than set up a separate scale each time a new lot of thromboplastin is prepared as urged by Allen,<sup>1</sup> many workers choose

to report prothrombin levels in terms of the clotting times or "prothrombin time." Campbell, *et al.*<sup>6</sup> and Link<sup>12</sup> and his co-workers found that diluting plasma to 12.5% of normal before determining its "prothrombin time" resulted in a more sensitive reflection of variations in the prothrombin level.

The one-stage method utilizes an excess of thromboplastin, an optimum amount of calcium, and a constant temperature to render the clotting process more uniform. The normal buffering action of the plasma also serves well to maintain a satisfactory pH range, and the blood colloids probably serve further to stabilize the reaction. There are numbers of known factors, however, and no doubt some as yet unknown, which are left uncontrolled and may be the cause of wide variations in expected prothrombin estimates by the one-stage method.

Among the known variables are differences in the rate at which prothrombin is converted to thrombin. This varies from species to species and often among individuals of the same species.<sup>17,25,26</sup> Fantl and Nance<sup>3</sup> suggested that normal coagulation depends not only on a normal prothrombin but on a prothrombin accelerator as well. Ware, Guest, and Seegers<sup>22,23</sup> have recently isolated a plasma fraction which has such a property and suggest that it may be an important factor in certain pathologic blood clotting tendencies.

It has been known for some years that normal human serum contains a

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factor which neutralizes the active principle in placental toxin. Recently Schneider<sup>16</sup> has suggested that the toxic factor may be thromboplastin and its inactivator antithromboplastin. He presents evidence to indicate that this latter factor is increased during pregnancy. In what other clinical conditions it may vary and what role, if any, it may play in influencing the clotting time in the one-stage prothrombin determination is unknown.

Antithrombin may vary widely in different plasmas,<sup>13</sup> and variations in the heparin content of blood have been observed.<sup>3,4</sup> The catalytic action of heparin on antithrombin<sup>18</sup> may be of real clinical importance in patients with abnormal heparin levels.

Fibrinogen levels are known to vary under certain conditions<sup>9,10,21</sup> though Witts<sup>27</sup> found that the plasma fibrinogen must fall to less than 30% of normal before it materially affects the "prothrombin time." Fibrinogen changes in dogs given dicumarol have been reported.<sup>11</sup>

The results of the one-stage prothrombin determination then may be influenced by one or more of the above mentioned factors and possibly others as yet unknown. Diluting the plasma to 12.5% or less before the determination is made may modify the influence of these factors to some extent:

The "two-stage" determination as described by Warner, Brinkhous and Smith,<sup>24</sup> by utilizing the two-stages in which blood normally clots, eliminates certain of the above mentioned factors, namely, the variation in the conversion rate of prothrombin and variations in the plasma fibrinogen. By providing for high dilution of the plasma, it neutralizes the antithrombin factor. Heparin may affect both the one-stage and two-stage tests in that it interferes with the conversion of prothrombin to thrombin. Antithromboplastin is highly sensitive to dilution,<sup>13</sup> and diluting the plasma in the experience in this laboratory with the

two-stage determination renders that factor inactive during the procedure.

The important consideration in the control of dicumarol therapy is the maintenance of a safe, effective level of plasma prothrombin. A safe level has been taken to be that at which bleeding does not occur. The importance of this is emphasized by the reports of fatal hemorrhages during its administration. The possible deleterious effects of the drug administered over a period of years have not been determined. The effective therapeutic level for the prevention of intravascular clotting, or the extension of clots already formed, has not been definitely established, and there is at present no evidence that there is a therapeutic level at which intravascular clotting can absolutely be prevented. Several investigators<sup>7,15,20</sup> have reported a lowering of the incidence of experimentally produced thrombi in dicumarolized animals as compared to control series, and there are numerous clinical reports of a lowered incidence of post operative thrombo-embolism in patients given dicumarol prophylactically. Allen<sup>2</sup> recommends a therapeutic range of between 10 and 30% using the one-stage method for prothrombin determination. He has observed that intravascular clotting rarely occurs when the prothrombin level is less than 30% of normal, and bleeding is rare when the prothrombin is above 10%.

**Present Study.** The purpose of the present study was to establish, if possible, a safe effective level at which the prothrombin can be maintained over an indefinite period of time, and to determine the methods best suited for such maintenance. Since the present confused state of terminology makes it difficult to know the effective level, it seemed reasonable to maintain the prothrombin in the lowest bracket which proved to be safe, thus allowing the utmost benefit from the drug. Previous

use of both the two-stage and the one-stage methods has shown the former to be more sensitive in reflecting changes in the plasma prothrombin.

This report represents a study of 99 patients under dicumarol therapy. In 91 of the cases, both the orthodox Quick test<sup>14</sup> and the two-stage test were used. The thromboplastin in the Quick test in all instances gave a normal control clotting time of 11 to 12 seconds. In 14 cases, the modification of the Quick technique, as suggested by Campbell and his associates;<sup>6</sup> that is, the "12.5% plasma" technique was used. In these cases the same test was made on 5% plasma to see if the use of a still more dilute plasma would result in more sensitive changes. The shortest period of administration of the drug was 4 days and the longest 23 months. The average time was 60 days, though the several prolonged periods bring this average to a somewhat higher figure than the usual period of therapy. Four to 6 weeks have been the arbitrarily established period for the usual case of acute thrombosis, this being extended if the individual case seemed to warrant it.

**Method of Administration.** When the patient is first seen a prothrombin determination is made, and if it is found to be above 80% (two-stage), an initial dose of 300 to 500 mg. of dicumarol, depending on the size of the patient and the original prothrombin level, is given. The second day 100 to 200 mg. are given. Prothrombin determinations are repeated 2 days after the initial dose, and the selection of subsequent dosages is based on the prevailing prothrombin levels. At the present time determinations are made before the initial dose of dicumarol, 48 and 72 hours after that dose, and then at intervals of 2 days until the prothrombin drops to therapeutic levels. This usually requires 3 to 7 days but may take longer. Determinations may then be reduced to twice weekly, later on to once a week. As will be discussed later, a bracket of between 10 and 20% plasma prothrombin (two-stage) is regarded as ideal in each case but is difficult to maintain. In most cases, however, variations over a period of time may be limited to between 5 and 35%. In hypertensive patients, an effort is

made to keep the level in the neighborhood of 30%. When the prothrombin drops below 5%, as frequently happens in the early days of treatment, a urine specimen is examined daily for blood. The drug is not withdrawn and usually vitamin K is not given. The dose of dicumarol is reduced by 50 mg. for 1 or 2 days, depending on the prothrombin determinations, which are usually one daily or every 2nd day during this period. Usually the prothrombin returns to a level above 10% in a few days. Efforts are directed towards anticipating this rise and stopping it at the desired level. Bleeding is not necessarily expected at such low levels, but if it occurs the same procedure is followed. The one-stage test is of particular value at this point. If it shows a level of 10% or below, the safety margin supplied by the other blood clotting factors is known to be reduced and bleeding may be imminent. (Fig. 5). If a patient leaves the city for several weeks at a time, he continues to take dicumarol and sends samples of blood in at 7 to 10 day intervals. During weather other than that of hot summer days, the prothrombin is relatively stable in transit. From nearly any section of the country it can reach the laboratory within 15 hours from the time it is drawn. The common maintenance dose over a long period of time is 300 to 450 mg. per week, though patients may require greater or lesser quantities of the drug.

*Combined Use of Heparin and Dicumarol.* In 34 of the acute cases of intravascular clotting, heparin was used in the first 48 to 72 hours before the full effects of dicumarol could be expected. A discussion of heparin therapy is outside the scope of this paper, but it must be borne in mind that heparin interferes with the conversion of prothrombin to thrombin, and any blood sample intended to guide the dosage of dicumarol must be drawn after the effects of heparin have been expended.

*Comparison of Methods.* With the use of the two-stage test it has been possible in most instances to reduce the prothrombin level to a bracket of between 5 and 35% and, with an occasional level slightly below or above, hold it between these two levels. Figures 1, 2 and 3 are representative charts of patients easily controlled under di-



cumarol therapy, with little variation in dosage once a therapeutic level has been reached. In Figs. 1 and 2, one-stage, whole plasma, determinations are shown for comparison with two-stage readings. Figs. 3 and 4 show, in addition, the results of "prothrombin times" on 12.5% plasma. In many instances the prothrombin variations as measured by the different methods

sometimes fatal hemorrhages have occurred. The two-stage test, however, shows that the prothrombin has not varied greatly from the previous level, and no marked change in the dicumarol dosage was made. At the time of the next test, the results of the one-stage and the two-stage were again parallel. The reason for the marked variation of the one-stage in such instances is not

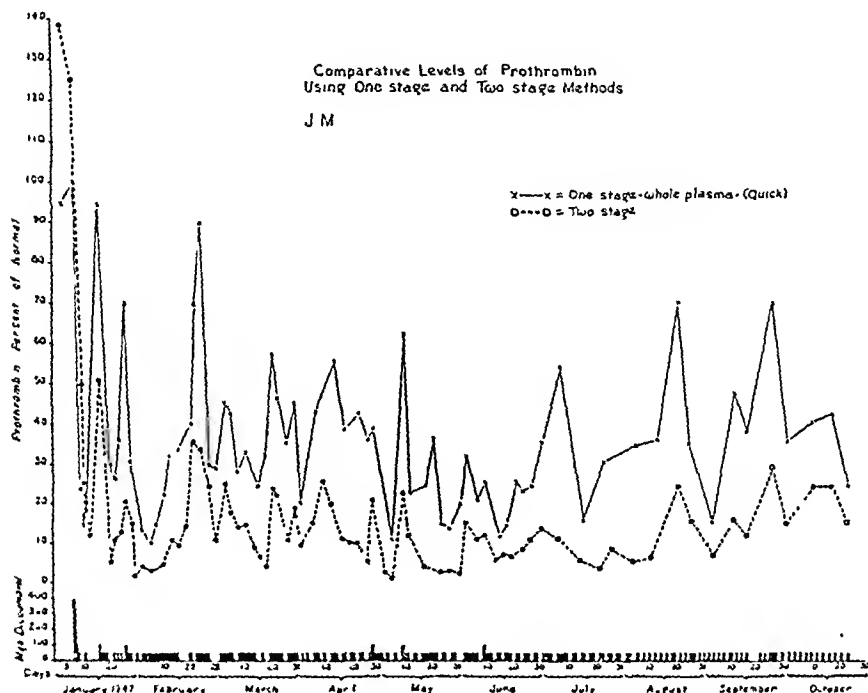


FIG. 1.—Comparative prothrombin levels, 1-stage and 2-stage methods, of a patient receiving dicumarol for 10 months. She was originally treated for a thrombophlebitis, and because she felt her multiple sclerosis was unimproved during the therapy, her physician maintained it for 10 months. Note the wide variation between the 1-stage and 2-stage prothrombin readings. Her sensitivity to dicumarol was determined while she was hospitalized during the early days of her thrombophlebitis, and she was later treated as an outpatient. There was no apparent objective improvement in her multiple sclerosis.

parallel each other, but this parallel is not consistent. For example, in Fig. 1 in several instances the two-stage method shows a level of between 20 and 30%, while the one-stage registers a level of between 60 and 70%. If the one-stage test were guiding the therapy, one would be prompted at such points to give a large dose of dicumarol which would likely lower the prothrombin to a dangerous level. In all probability it is in such instances that serious and

entirely clear, but one or more of the factors mentioned earlier may have been responsible. Likewise, the prothrombin estimates using 12.5% plasma do not show a uniform variation as compared to the two-stage or even the one-stage whole plasma determination (Figs. 3 and 4). Five % plasma was no more uniform than the 12.5% in reflecting prothrombin variations.

As mentioned above, 91 of the 99 cases were followed with both the one-

stage and two-stage tests. Most of the other 8 cases were at times checked with the one-stage as well as the two-stage determination, particularly when the prothrombin level fell to less than 10%. This was of value in estimating the summation of the various clotting and anti-clotting factors of the individual blood at a point where the patient might be in danger of hemorrhage from a prothrombin deficiency.

and an elevation of the prothrombin by diminution of the dosage or withdrawal of the drug or, in some instances, administration of vitamin K is indicated (Fig. 5).

**Bleeding Hazard.** Bleeding occurred in 15 cases, the most common site being the urinary tract. In 13 of the 15 patients, the prothrombin level was between 1 and 11% (two-stage) when the bleeding became apparent, and

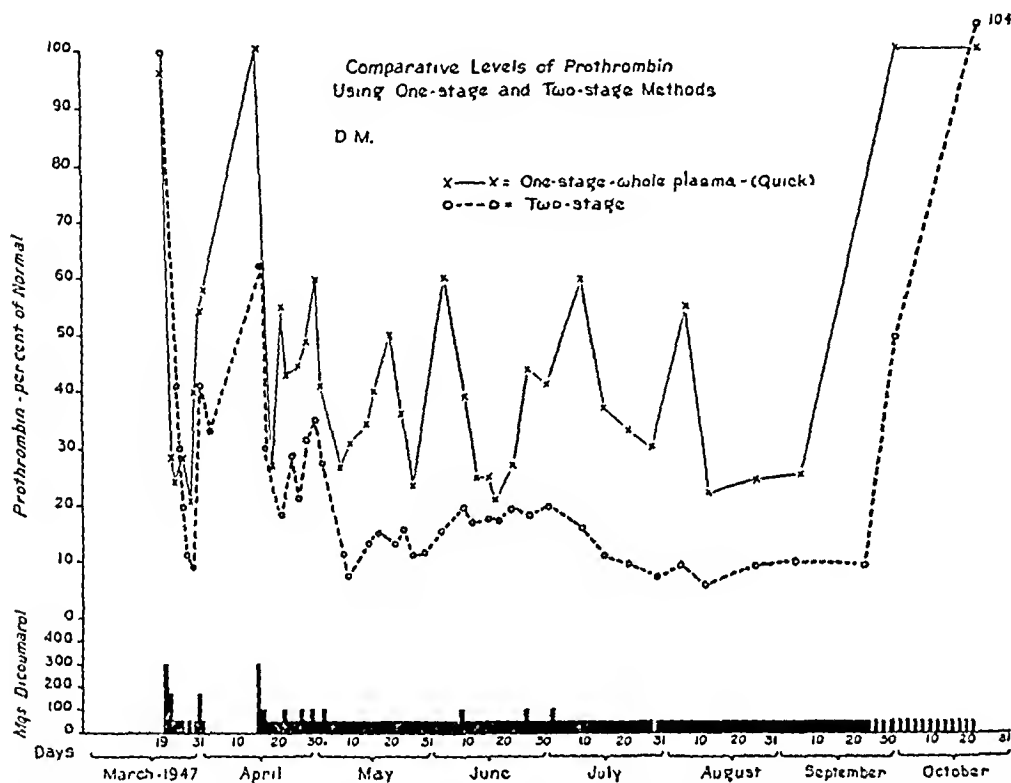


FIG. 2.—Prothrombin levels of a patient on dicumarol therapy, easily controlled for months with weekly prothrombin determinations. A phlebothrombosis developed following minor injury to the leg, and the patient improved on heparin and dicumarol. He left the hospital after 12 days and therapy was discontinued. Symptoms recurred 2 weeks later, and heparin and dicumarol were re-instituted. A thrombus in the great saphenous vein remained palpable and somewhat tender over the ensuing 5 months, during which his prothrombin was maintained within a bracket of 7 and 19%. On 3 occasions the prothrombin according to the 2-stage method stood at 15, 16 and 9% respectively, while the 1-stage whole plasma test showed levels of 60, 59 and 55% respectively. There was no bleeding at any time and no residual signs or symptoms after therapy was stopped.

Even though this prothrombin as measured by the two-stage method might stand at 4%, a one-stage determination showing 10% or more would indicate that there were sufficient compensating factors to make bleeding unlikely (Fig. 3). On the other hand, a level of less than 10% of both methods is a warning that bleeding may be imminent,

stopped when the prothrombin rose to between 15 and 20%. In the other 2 cases bleeding followed trauma, the prothrombin being 36% at the time in both patients. In 13 cases bleeding stopped following reduction of the dosage of dicumarol. Two patients received vitamin K to raise the prothrombin level. Three patients with levels of be-

tween 5 and 20% have fallen without sustaining bruises. There was no instance of fatal hemorrhage in this series.

Seven patients have been on controlled therapy during menstruation, 5 of them having had prothrombin levels between 5 and 25% at the time. In one case, the menstrual period was one day longer than usual. The intensity of bleeding was not changed. Five patients noticed no variation from the

the prothrombin is above 50%, it does occur and may well have been a factor in this instance.

*Effectiveness of Dicumarol Therapy.* The effectiveness of dicumarol in preventing thrombosis or its complications is difficult to evaluate in that adequate controls cannot be conveniently set up.

In this series it was used as a prophylactic measure in 12 cases. Of the 12 cases, 1 developed thrombophlebitis

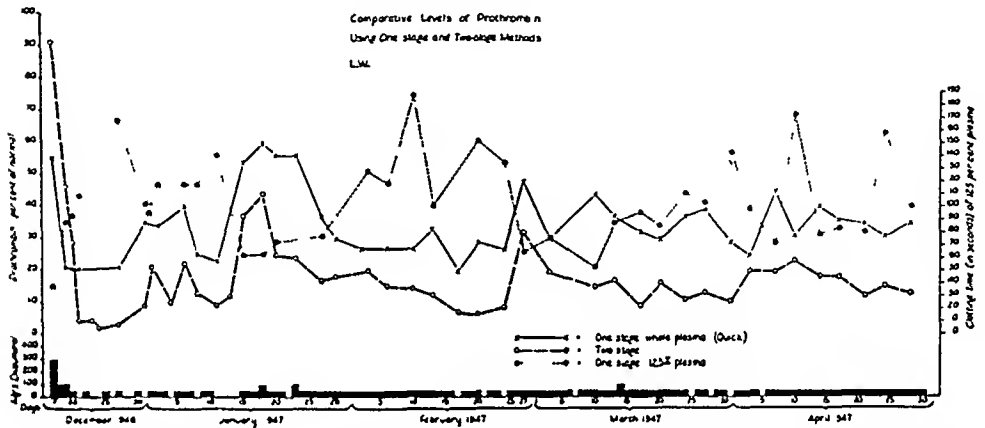


FIG. 3.—Prothrombin levels of a patient under dicumarol therapy because of an acute, severe thrombophlebitis of the right leg. The results of the whole plasma techniques (1-stage and 2-stage) are expressed in per cent of normal on the left hand, and the results of the 12.5% plasma are recorded in seconds,—the right hand ordinate. In the early stages, the results of the 1-stage whole plasma technique closely parallel at a somewhat higher level those of the 2-stage test. Later, this parallel disappears, the 1-stage showing a rise, while the 2-stage shows a drop in prothrombin level. The prothrombin time of 12.5% plasma in general shows a rise when the prothrombin level according to the whole plasma 1-stage test falls, but the findings are erratic and not suitable for dicumarol therapy control. Note that while on December 21 the prothrombin, 2-stage, fell to 2% of normal, the 1-stage test showed a 20% level, indicating that there were sufficient compensating factors in the blood to prevent bleeding. The patient did not develop bleeding during his course of therapy.

normal. One patient developed microscopic hematuria when her prothrombin was 7%. It had stopped 2 days later when the prothrombin reached 24%. Five days after this, she began to menstruate excessively. Her prothrombin level was 53% at the time. During the next 60 hours she was given 24 mg. of vitamin K parenterally by her physician. Excessive bleeding had stopped by the time the vitamin was started. Three days after the last dose her prothrombin level was 57%. Such excessive bleeding was out of the ordinary for this patient, and while it is unusual for bleeding to be present when

postoperatively. She was uncooperative and administration of the dicumarol was not satisfactory. When her thrombosis occurred, the prothrombin level was 66%. No sign of thrombosis occurred in the other 11 cases.

Twenty-one cases of acute coronary thrombosis were dicumarolized. There were no deaths, and none developed other thrombo-embolic phenomena. One patient with myocardial decompensation, who earlier had had anterior and posterior myocardial infarctions, was treated with dicumarol after he developed phlebothrombosis of the left leg and signs of a small pulmonary

embolus. Before his prothrombin reached therapeutic levels, signs of thrombosis developed in the other leg. Swelling of both legs disappeared after 2 weeks, no further emboli developed, cardiac function improved, anticoagulant therapy was discontinued and the patient left the hospital. Sixteen days

bolus. He had had no dicumarol for 34 days.

Acute thrombophlebitis or phlebothrombosis of the lower extremity without signs of embolism were treated with anticoagulant therapy in 43 instances. Papaverine was used in a few cases, but the treatment otherwise was

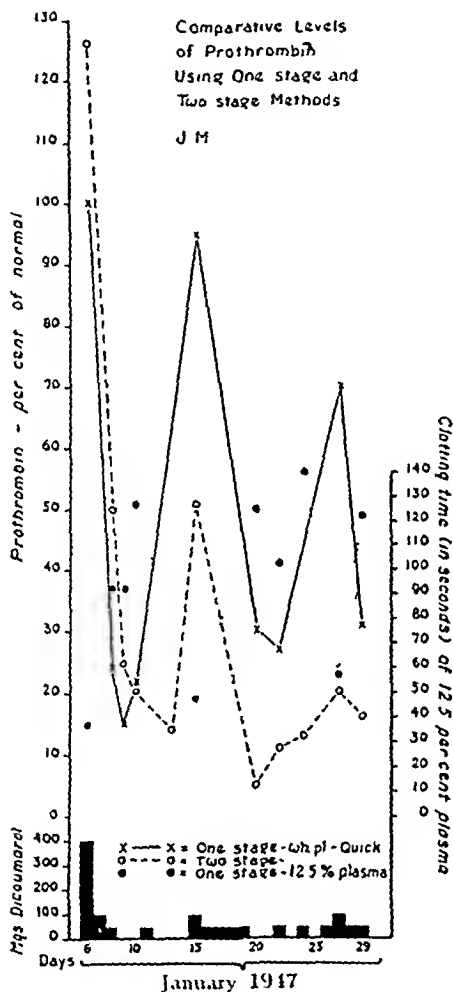


FIG. 4.—Comparative prothrombin levels according to the 1-stage whole plasma technique, the same technique using 12.5% plasma and the 2-stage technique. The results of the whole plasma techniques (1-stage and 2-stage) are expressed in per cent of normal, on the left hand, and the results of the 12.5% plasma method are expressed in seconds,—right hand ordinate. Note that on January 6, 15 and 27 the "prothrombin time" of the 12.5% plasma is 37, 48 and 57 seconds, respectively, relatively near one another. The 2-stage method at these points shows a level of 126, 51 and 20% respectively, relatively divergent values. This chart represents the first month of treatment of the patient shown in Fig 1, and as will be noted there, her prothrombin (2-stage) remained fairly well stabilized over a period of time. Attempts to order dicumarol on the basis of the 1-stage method using either whole or 12.5% plasma might have led to undesirable and serious results.

after the last dose of dicumarol, he developed a thrombus of the right femoral vein, and 4 days later of the left. He died suddenly 2 weeks later of what appeared to be a cerebral em-

bed rest. The legs were not elevated or immobilized. One case of acute thrombophlebitis of the abdominal wall veins was treated likewise. The patients were kept in bed until the swelling disap-

peared in the instances of phlebothrombosis, and until the pain and redness were gone in the thrombophlebitis cases. There were no instances of embolism. Three cases of thrombophlebitis of only the superficial veins at the time anticoagulant therapy was started did not progress to involvement of the

tient a sizable optico-ciliary anastomosis was observed after 8 months of dicumarol therapy.

Thirteen cases of embolism, single and multiple, were treated in patients with phlebothrombosis (8), auricular fibrillation (3), bacterial endocarditis (1) and no definitely known source of

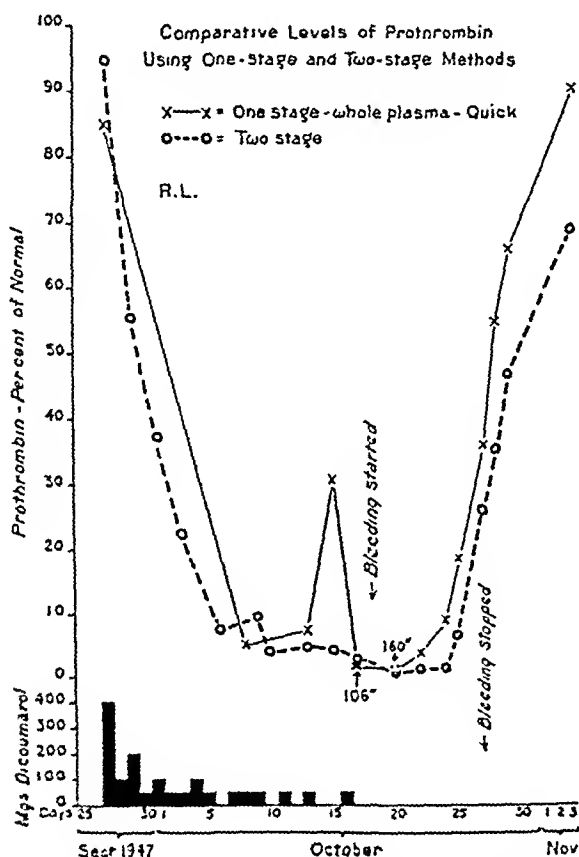


FIG. 5.—Rapid response to dicumarol in a patient relatively sensitive to the drug, and a prolonged bleeding despite withdrawal of the anticoagulant. The 50 mg. dose of dicumarol was given on October 18 by error and gross hemorrhage was observed on October 17. Bleeding continued and the prothrombin level showed little change until October 25. On October 26, because of troublesome dysuria, 3 doses of 19.2 mg. each of Bykam were given intravenously at intervals of 2 hours. Bleeding stopped the following day.

deep veins. None of the cases of phlebothrombosis developed into thrombophlebitis.

Ten cases of thrombosis of the central retinal vein were given dicumarol, 2 of them receiving heparin as well. There was no progression of the loss of vision in any case, and improvement occurred in all cases. In one pa-

tient the emboli (1). In 11 cases there were no further emboli as long as the patients stayed on treatment. One patient, controlled with difficulty, had repeated small pulmonary emboli from what was considered to be a mural thrombus in the heart. Two of these developed when her prothrombin was at 11 and 44% respectively, and a phle-

bothrombosis of the left leg came on when her prothrombin was 79%. What was clinically a splenic infarct developed when the prothrombin was 10. Another patient had what appeared to be repeated small pulmonary emboli when his prothrombin was 34%. No further ones occurred when it dropped to 26% or below.

One patient with Parkinson's disease was treated with dicumarol over a period of 42 days without apparent benefit.

Four cases of multiple sclerosis were treated with dicumarol therapy, one for as long as 11 months. Three showed no improvement, and the other who is still on therapy at the writing of this paper has shown subjective improvement.

Three patients with cerebral thrombosis were treated with dicumarol. One, a man of 68, had 2 episodes of paralysis in 2 years. He was placed on dicumarol therapy following the first attack and completely recovered. Two years later he had a recurrence and was again placed on dicumarol therapy. Recovery was again complete, and he has been on dicumarol therapy since that time, a total period of 23 months. He has had no recurrence. A second patient, a man of 82, improved following his cerebral accident and left the hospital after 7 days. Dicumarol was discontinued 6 days following this. Six months later he again developed cerebral thrombosis and was again placed on heparin and dicumarol. His condition again improved, and he was discharged after 55 days without continuation of therapy at home. Six weeks later he died suddenly, and at autopsy a large pulmonary embolus and phlebothrombosis of the right hypogastric vein were found. Permission to examine the head was not obtained. A third patient, a woman of 74, has shown steady improvement after 6 weeks of dicumarol therapy following cerebral thrombosis.

This series of cases is too small to be a basis for conclusion as to the value of dicumarol as a therapeutic and prophylactic agent. However, of the 99 cases included here, 94 were treated actively or prophylactically for thrombotic or thrombo-embolic conditions. Of these, three (3.3%) had further thrombo-embolic phenomena while on dicumarol, 1 while under what was considered to be adequately controlled therapy. The other 2 were not satisfactorily controlled when the thrombus or embolus developed. The results support the work of others who have reported a decrease in thrombo-embolic phenomena in patients receiving this type of treatment.

*Prolonged Dicumarol Administration.* In this series, 6 patients received dicumarol longer than 4 months, 4 for over 6 months, 3 for more than 9 months, 2 for 12 months, another longer than 20 months, and one patient took it for over 23 months. They were controlled by tests at weekly intervals, and in the long term cases the intervals were as long as 2 weeks.

Neither these nor any of the other patients under treatment for shorter periods of time, showed any signs of toxic reaction to the drug. Occasionally, a patient vomited when large doses—300 to 400 mg.—were taken at one time.

It is of interest that one patient in this study required as little as 100 mg. of dicumarol weekly as a maintenance dose, while one received as high as 2800 mg. a week without being adequately controlled. The factors influencing these wide variations in tolerance to the drug are not clear. The influence of drugs such as the methylxanthine will be discussed in a later paper.

*Summary and Conclusions.* 1. Ninety-nine patients were treated actively or prophylactically with dicumarol, and in 34 cases heparin was also used.

2. With the use of the two-stage prothrombin determination, it was possible accurately to maintain the prothrombin level within a desired range over a period of months, with a maximum variation in some instances of 15%.

3. Fifty (50.5%) of the cases were treated as outpatients, most of them on weekly prothrombin determinations. The treatment period varied up to as long as 23 months. Some of the patients were out of the city for weeks at a time, and blood samples were sent to the laboratory for control purposes.

4. One-stage prothrombin methods (whole plasma, 12.5% and 5% plasma) were compared with the two-stage method. In all cases, there were wide variations between the methods used.

5. The two-stage method is regarded as a more accurate and a safer method for the control of dicumarol therapy than any of the other methods used. The one-stage method is of real value, however, in estimating the summation of the clotting factors in an individual blood, particularly at a time when the prothrombin as measured by the two-stage test is below 10%.

6. Bleeding occurred in 15 (15.1%) of the 99 cases given dicumarol. In 13 of the 15 patients, the prothrombin level was between 1 and 11% (two-stage) when the bleeding became apparent, and stopped when the prothrombin rose to between 15 and 20%. In the other 2 cases bleeding occurred following trauma, the prothrombin being 36% at the time in both patients. The urinary tract was the most common site of bleeding.

7. In those patients in whom bleeding developed, withdrawal of the drug for 1 or sometimes 2 days was sufficient in most cases to bring the prothrombin level to within safe limits. Since the dicumarol therapy was accurately controlled, the individual patient's prothrombin level was usually not far below his bleeding threshold. In two cases, vitamin K was given to raise the prothrombin level which responded promptly, and the bleeding stopped in less than 24 hours in both instances. There were no cases of fatal hemorrhage in this series.

8. Three (3.3%) of the 99 patients on dicumarol therapy showed evidence of further thrombo-embolism. Of these, 1 showed such evidence while the patient's prothrombin was considered within the therapeutic range. In the other cases, it was above that range. The results of this study support the conclusions of other workers in the field that the use of dicumarol is of value in the prophylactic and active treatment of thrombo-embolic conditions. The results also suggest that a range of 10 to 30% (two-stage) is a safe, efficient level for the maintenance of plasma prothrombin.

9. Other than bleeding, no toxic effects of dicumarol were observed. The prothrombin level promptly returned to normal when the drug was discontinued.

Miss Luellen Dale and Mrs. Angelina Vicencio contributed valuable technical assistance during this study.

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## PROGNOSIS OF PNEUMONIA\*

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THERE is a number of well known factors which have an influence on the prognosis of pneumonia, some of them are for good, others for evil. We wish to call attention to some of these factors.

Communities vary in the severity of their pneumonias, and in certain cities, Pittsburgh, for example, the death rate has always been known to be high: in fact, as compared with New York, almost double until very recent years after the introduction of chemotherapy.

In severe influenza epidemics, as in 1918, the prognosis of pneumonia is very much worse. In the winter of 1936-37 we had a small epidemic of rather virulent influenza with a subsequent rise in our pneumonia death rate.

There are some host factors which appear to have an evil influence on the outcome of pneumonia, namely, old age, chronic alcoholism, and neglect of the acute pneumonic infection after it has developed. Frequently, we see all of these factors combined in the same patient. It is our opinion that the last, the neglect of the pneumonia, is by far the most important and it is common experience to have in the pneumonia service patients with pneumonia who had been walking about the streets for a variable number of days. It is well to remember the path-

ologists' observation in this regard, namely, that at autopsy in cases of sudden death on the streets in the pneumonia season of the year, in about 15%, the cause of death is pneumonia. We usually have in each year a few patients who die within a few minutes to a very few hours after admission to the hospital. Such neglected cases have little importance as regards therapy, and it is misleading not to separate this group from those who have been available for treatment at least 24 hours in the hospital. Today very few, other than neglected cases of pneumococcic pneumonia, die.

The rate of the pulse we find to be the most reliable clinical sign as to the prognosis of the pneumonia. A gradually rising pulse rate to beyond 120 per minute is not good. The opposite also tends to hold true, namely, one rarely sees a fatal outcome in a pneumococcic pneumonia patient with a pulse rate consistently under 100. We do not include children in this group nor, of course, postoperative atelectasis.

The finding of pneumococci in the blood culture has always been in the past the most exact factor from which to make a prognosis,<sup>1,2</sup> but today penicillin cures many of the bacteremia cases which formerly died. The blood culture must be taken before any penicillin has been given because it does

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not appear to take very much penicillin to change a positive to a negative culture. We would further emphasize the importance of making bedside blood agar plates so as to have bacterial colony counts. Over a period of a number of years we have yet to see a recovery from pneumonia where 15 or more colonies were counted on the plate from 1 cc. of blood made immediately at the bedside in cases where no specific treatment, serum or chemical, was given. In our opinion there is not much value in taking blood

cases with 18.7% of them showing a leukocyte count of 10,000 or less. The mortality was 61% in this small group of cases. They had a very high bacteremia rate of 46%. In our experience this was the rule in prognosis for pneumococcic pneumonia patients with low leukocyte counts. But during the past 21 months, 1946-48, the figures are very different. In this period we had 169 cases with 43.2% of them having leukocyte counts below 10,000, and a mortality of only 7%. The bacteremia incidence of the group was

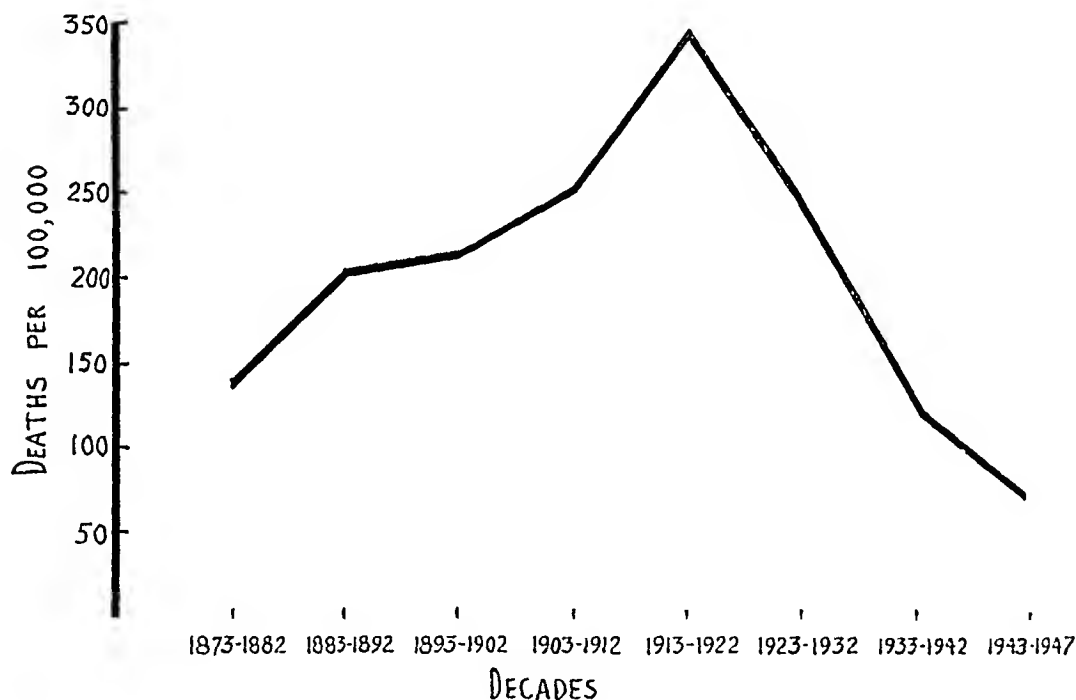


FIG. 1.—Pneumonia deaths in Pittsburgh. Average rates per decade.

cultures in pneumonia if plates are not made. This is particularly true if one is studying any special form of therapy, as it makes the reading of the results of treatment easier and more accurate.

A leukocyte count in pneumococcic pneumonia below 10,000 has usually carried with it a serious prognosis. However, in the past 21 months, 1946-48, this has not been true in our cases, as the following data from our records would indicate. In 1935-36 we had 81

34% which certainly is an index of the virulence of the infection. The low mortality we believe is due entirely to penicillin, but this does not alter the fact that in this large group of cases with low leukocyte counts a bad prognosis could not be made from the leukocyte count itself, and therefore, during the past 21 months the leukocyte count has had no prognostic value. The frequency of low leukocyte counts in pneumococcic pneumonia, in our opinion, is not due to the patient's

resistance, but to some unknown factor in the type of the infection. It has been noted by others,<sup>6,8</sup> in different parts of the country.

Finally, the most important influence for good on the prognosis of pneumonia today is penicillin. The following charts show some of these points on prognosis, particularly the results of treatment with penicillin.

Fig. 1 indicates a period of 75 years from 1873 to 1947. It is divided into 10 year periods except for the last one which is only 5 years. In each period

figure of 139. Certainly, at that time there was no specific treatment for pneumonia, so the low mortality for that period must have been due to a milder infection. For the next 50 years, however, 1883 to 1932, the average year in each decade was never below 200. The great epidemic of influenza in 1918 accounts for the high peak of 343. From 1933 to 1942 there is a fall to 124 and for the last 5 years to 1947 the very low average figure for the year was 77. During the last 15 years the fall in the death rate has been defi-

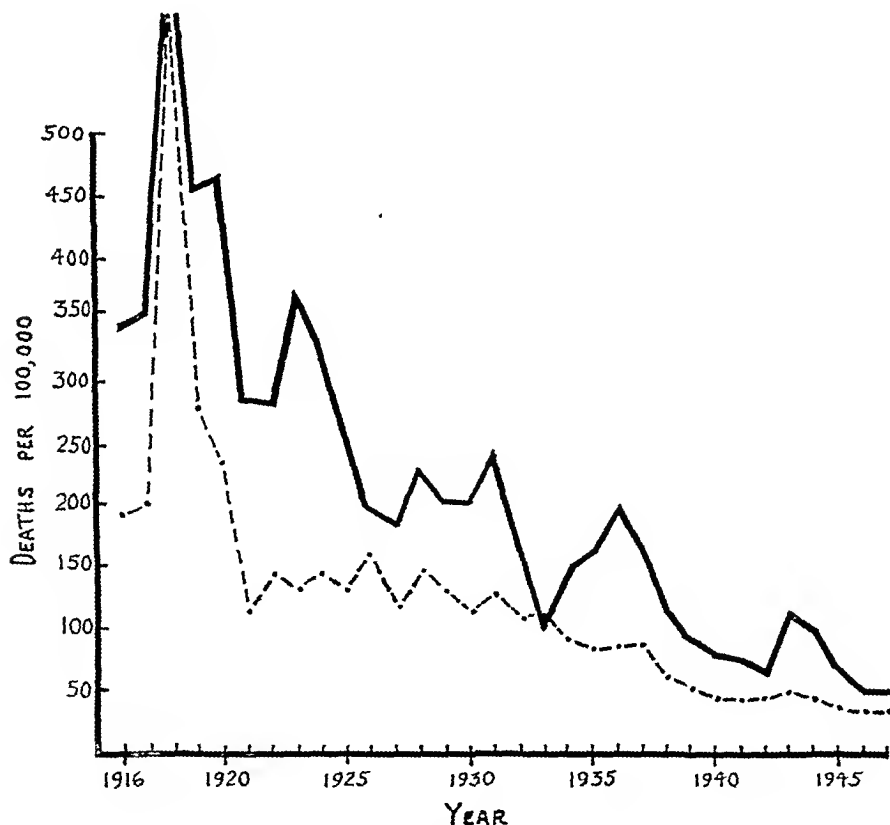


FIG. 2.—Pneumonia deaths per 100,000. 1916-1947.

the years are averaged. The chart is made from statistics from the Department of Health, Pittsburgh,<sup>6</sup> and represents the deaths from pneumonia per 100,000 population over this period of time. We would call attention to the first decade, 1873 to 1882, with the low

nite. Serum was made more available by the City Health Department from about 1934 to 1938, and probably made some impression on the mortality figure. Sulfapyridine became available in 1939, and from that date on chemotherapy, including penicillin in the past

2 years, is chiefly responsible for the low mortality figure. However, in the early part of this last decade and a half, 1933 to 1938, the question of a milder infection may have to be considered as a possibility, since we do not believe that anti-pneumococcic serum was used widely enough to be entirely responsible for the fall in that period.

Fig. 2 indicates the difference in the pneumonia death rates in 2 communities, New York and Pittsburgh. The charts are made from statistics from the Department of Health of the 2 cities. Over a period of 32 years

1933 is the only year when our mortality rate was lower than New York, 105 to 108. Our pneumonia, in the clinical sense, was mild that year. There was, of course, no chemotherapy and not too much serum was used, as the City Health Department at that time was not supplying free serum for pneumonia cases. The low mortality figure in 1933, therefore, was spontaneous. In that year of the depression the Pittsburgh mills were not running and we had relatively little smoky atmosphere and much unemployment. We do not know exactly if these factors



FIG. 3.—Mortality rate in pneumonia at Mercy Hospital. 1925-1948.

the death rate from pneumonia in Pittsburgh has always been higher than that of New York, except for one year. In the earlier years it was often double, but since chemotherapy the figures are more nearly equal. Our rates have dropped from 350 in 1916 to 54 in 1947, while the New York figure was 200 to 37. We wish to note the excessive peak in 1918 which was 1222 for Pittsburgh and 603 for New York;

had any influence on the mortality rate of pneumonia. The rise in 1936-37 followed a sharp but small epidemic of influenza beginning Christmas week, 1936. From 1939 the sulfonamides had their influence on the curve and in 1945 penicillin was added. Probably in the past 2 years much more penicillin was used generally in Pittsburgh. Again there is the suggestion that in 1938, the year before the wide use of

sulfapyridine, the mortality rate was falling and possibly this was due to a mild infection rather than to any effects of specific treatment.

Fig. 3 shows the mortality rate in the pneumonias in our own wards at the Mercy Hospital, Pittsburgh, from 1925 to 1948 (to April 1st). There was very little change in mortality until 1937-38. We had used dextrose from 1925-30 with no change in the prognosis. The first fall in 1937-38, we

lan therapy began. Since 1946 we have used only penicillin over a period of 21 months, and the low mortality rate we feel is due to this medication. With a 43% mortality in 1925, the death rate has now fallen to 11% for all cases admitted, even if they died a short time after entering the hospital, or 6% if they were treated for at least 24 hours with penicillin. No children are included, while many cases were over 60 years of age.

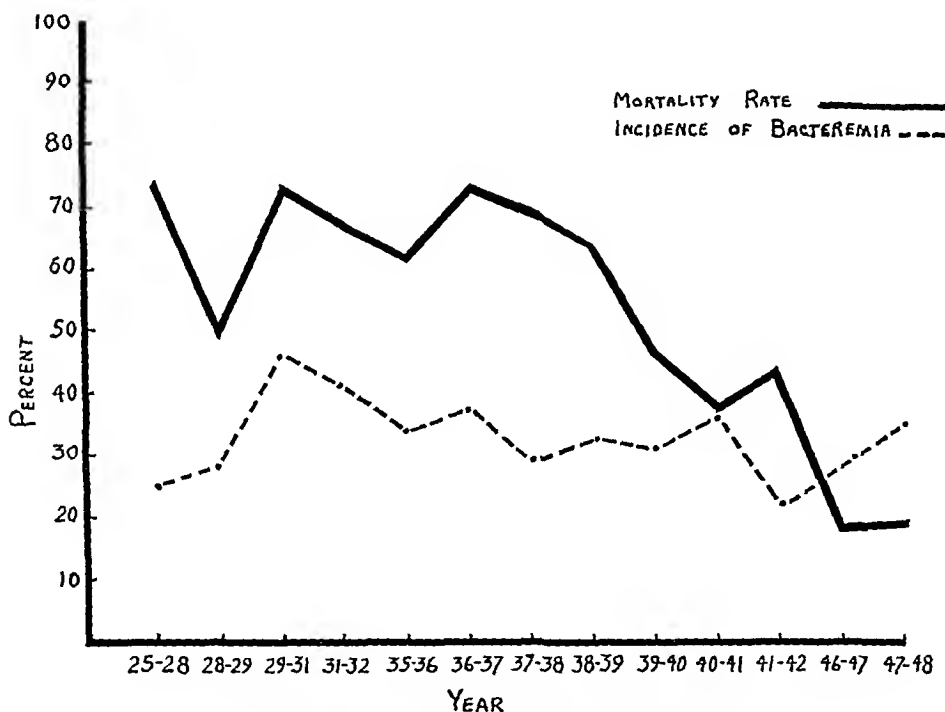


FIG. 4.—Mortality rate in pneumococcus bacteremia. 1925-1948.

believe, was associated with hydroxyethylapocupreine,<sup>4,5</sup> which we began to use in 1935-36, but only in adequate amounts from 1936 until 1942. Sulfapyridine was added in 1939. The fall in mortality curve, 1937-42, was therefore, due to the chemotherapy which in our wards was about equally divided between the quinine derivative, hydroxyethylapocupreine, and the different sulfonamides. The rise in 1943 and 1944 preceded a final fall after penicil-

In Fig. 4 the mortality rate of the pneumococcus bacteremia cases is shown, as is also the incidence of the bacteremia over the same period of time, 1925 to April 1st, 1948. The marked fall since 1938-39 is the main point to note as in the earlier years, up to 1937, the mortality rate was about 70%, while in the past 21 months 1946-48, the deaths were 19% with all cases counted who were admitted and 11% of bacteremia cases who had peni-

cillin for at least 24 hours. Note that the incidence of bacteremia has not varied very much and in particular with the marked fall in deaths during the past 21 months the incidence of bacteremia was actually higher, reaching 35% of cases. The fairly constant bacteremia incidence is suggestive that there has not been a great change in the virulence of the infection over this period of time. During the 3 winter months of 1948, January, February and March, we had an incidence of 40% bacteremia with Types I and II com-

chemotherapy. The colony counts above 100 per 1 cc. of blood are listed, and it is to be kept in mind that all were recovered cases. The large number in the penicillin column is noteworthy and in this group we would call attention to 3 of them especially, 123, 2260, and 247. This group of 3 cases was treated by mouth with penicillin.<sup>2,7</sup> That they recovered is proof of the value of this method of therapy. We have used this method for the first 3 months of the year 1948 in most of our cases and it is now our opinion

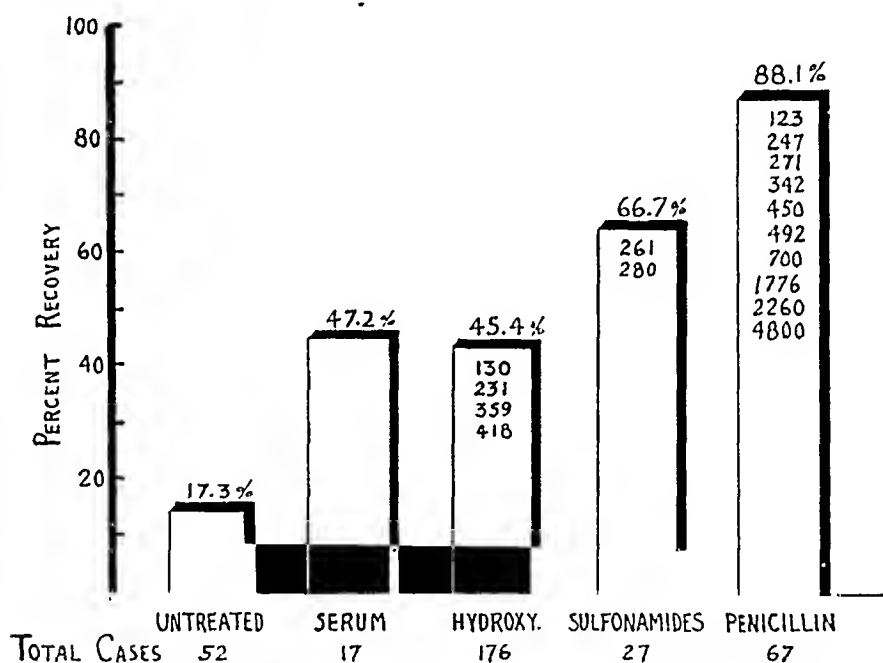


FIG. 5.—Pneumococcus bacteremia recovery rate. Colony counts above 100 listed. 1935-1948.

prising 90%. We have never seen more toxic pneumonias and yet the response to penicillin was remarkable.

Fig. 5 shows the recovery rate in bacteremia cases both non-specifically treated and specifically treated cases. Anti-pneumococcus serum, the quinine derivative hydroxyethylapocupreine, sulfonamides and penicillin were the specific measures used. The data were taken from 1935 to 1948 (to April 1st). The untreated cases were in the early years of 1935-37, as since then all cases in the hospital have had

that for pneumonia the giving of penicillin by mouth is the method of choice. A comparison of oral and intramuscular penicillin in pneumonia cases is as follows: oral, 52 cases with 4 deaths (7.7%). Of these, 24 cases had bacteremia with 3 deaths (12.5%). The intramuscular injection group had 159 cases with 10 deaths (6.3%), while 43 of them had bacteremia, with 5 deaths (11.6%). The 2 methods, therefore, showed about the same results. (This work will be published in another article.) In non-specifically treated bac-

teremia cases (symptomatic therapy only) we have never seen a patient with a colony count above 15 recover. The recovered cases with colony counts below 100, which are not listed, were naturally much more frequent. The largest group of the bacteremia cases, however, were those showing pneumococci growing only in the broth culture.

Conclusions. 1. The prognosis of pneumonia in Pittsburgh for many years has almost always been grave. It has, however, very markedly improved during the last few years due to chemotherapy. In our cases of the past 21 months the prognosis has been decidedly good.

2. Penicillin is the chief reason for the good prognosis.

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# THE EFFECT OF LIVER DYSFUNCTION ON THE RESPONSE TO DICUMAROL

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WITH the widespread use of dicumarol (3') Methylene bis (4-Hydroxy Coumarin) ) therapeutically and prophylactically, the existence of hyperreactors was early recognized.<sup>3</sup> After we began to use dicumarol on the Fourth Medical Division of Bellevue Hospital, we were struck by the number of patients with unusual sensitivity to the drug who had enlargement of the liver or other evidence of liver disorder. We undertook this study to ascertain to what extent the response to a test dose of dicumarol could be correlated with certain objective and laboratory evidences of hepatic dysfunction.

*Procedure.* Prothrombin time determinations were made by the Shapiro modification of the method of Quick, on whole plasma, using commercial thromboplastin manufactured by the Maltine Co. of New York City. Normal prothrombin times with this material ranged from 11 to 15 seconds. By reference to a conversion table, the values obtained with each sample were expressed in terms of percent of prothrombin activity.

One hundred male subjects chosen from among the patients of 2 medical wards were tested for prothrombin activity before and following a single dose of 100 mg. of dicumarol. No patients were selected whose undiluted plasma prothrombin activity was not normal. After dosage, daily prothrombin measurements were made until the prothrombin time returned to normal, or until 4 days had

elapsed with no change. In addition, most patients had cephalin flocculation tests and serum albumin-globulin determinations made in the central laboratories of the Bellevue Hospital. The results were tabulated and correlated with the clinical observations of the size of the liver below the costal margin, the presence and the amount of ascites, and the presence and degree of congestive heart failure.

*Results.* The results obtained in the 100 subjects are tabulated in Table I. Twenty-eight patients showed a fall in the prothrombin activity to less than 60% of normal. Of these, all but 2 had some evidence of hepatic disorder or congestive heart failure. The patients with the most profound depression of prothrombin had evidence of extensive liver damage such as ascites, positive cephalin flocculation tests, large livers or inverted albumin/globulin ratios. The lowest test of all was in a case of badly decompensated luetic heart disease.

While 93% of the 28 positive tests (below 60%) showed either congestive failure (11 cases), liver disease (12 cases) or both (3 cases), the 72 cases with tests above 60% showed only 17 (23.6%) with heart failure, 12 with liver disease (16.7%) and 3 (4.2%) with both, an overall percentage of abnormality of 44.5%.



In Fig. 1, the correlation between the positive tests and the clinical and laboratory evidence of liver disease is shown. Of 52 patients with enlarged livers (including 4 with massive ascites, rendering accurate measurement impossible) 24 (46.2%) showed positive tests. In contrast, in 48 patients in whom the liver was not palpable, there were only 4 positive tests (8.3%). Of 33 patients with congestive heart failure, 14 (42.4%) were hyper-reactors.

who sometimes showed prolongation of prothrombin time for over a week, there was no correlation with the other criteria of liver function. Patients with a marked sensitivity to dicumarol in terms of prothrombin depression might be normal the next day and, conversely, a slight depression of prothrombin might take several days to return to normal.

**Discussion.** The exact fashion in which dicumarol interferes with the

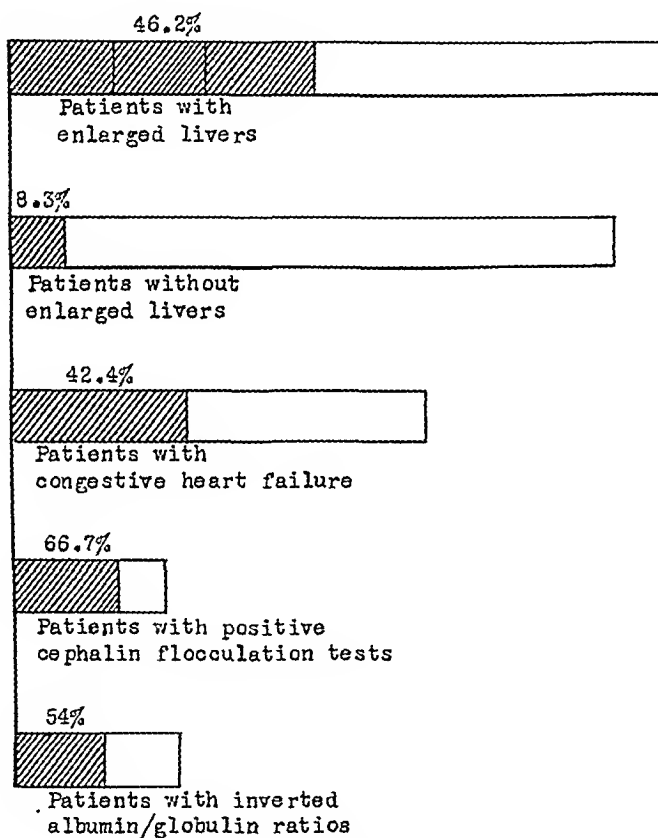


FIG. 1.—The proportion of hyper-reactors to dicumarol correlated with the size of the liver, presence of congestive heart failure, positive cephalin flocculation test, and inverted albumin/globulin ratio.

Of 12 patients with cephalin flocculation tests of 3+ or more, 8 showed prothrombin depression below 60%. Of 13 patients with inverted albumin/globulin ratios, 7 (54%) were positive.

The length of time that it took for the prothrombin time to return to normal was also studied. Aside from a few patients with advanced liver disease,

elaboration of prothrombin<sup>2</sup> is not understood. Fatal cases of dicumarol poisoning show no specific lesions in the hepatic parenchyma. Repeated and prolonged administration of the drug leads to no permanent depression of prothrombin, which is restored to normal rapidly upon the administration of vitamin K. If vitamin K and dicumarol

are given simultaneously the effect of the dicumarol is modified or completely inhibited.<sup>1</sup> The chemical structure of the two substances is so similar that biochemical antagonism seems a likely explanation of their relationship. Since it has been established that prothrombin is formed in the liver,<sup>6</sup> and the decrease in prothrombin time accompanying states of hepatic insufficiency is well known, it is logical that dicumarol should be more effective in patients with liver disease; and a diseased liver that was still functionally adequate to meet normal demands for prothrombin might be less able to resist the action of such a toxic substance as dicumarol.

Shapiro and his co-workers<sup>5</sup> gave test doses of 50 mg. of dicumarol to a group of patients with liver disease and found that only in cases with a pre-existing prolongation of the prothrombin time was there any significant change. We attribute our more positive results to the larger dose of the drug employed.

Our selection of patients might be criticized on the ground that mere palpability of the liver is no evidence of dysfunction, since a low diaphragm or variation in the flare of the ribs may push a normal sized liver down, or it may become ptosed through relaxation of the ligaments that normally support it. However, we know of no easy way to distinguish between many such livers and other livers actually diseased. Certainly, the palpability of the liver is the commonest clinical denominator of liver disorder, and should incite caution in the use of dicumarol.

An outstanding finding was the high incidence of congestive failure in the

positive reactors. It is difficult to believe that a liver distended to several centimeters below the ribs is not physiologically deranged, and bromsulphthalein excretion and other functional tests of the liver in congestive failure support this thesis.<sup>4</sup> With the increasing use of dicumarol in the treatment of coronary thrombosis and pulmonary embolism, it is important to recognize that congestive heart failure may decrease the tolerance to the drug.

Our work confirms once more the observation that the many functions of the liver may be interfered with independently of each other. We have had patients with marked evidence of liver damage who seem to have preserved well their prothrombin elaborating mechanism. We have also seen patients with alcoholic histories, large livers and no other objective evidence of liver dysfunction give strongly positive responses to 100 mg. of dicumarol. One such patient on a subsequent admission had developed a positive cephalin flocculation test. In conjunction with other liver function tests, the response to dicumarol may be of value in dating the onset and progress of liver disease.

**Summary.** 1. One hundred mg. of dicumarol were given to 100 patients and the effect on the prothrombin time followed.

2. Depression of prothrombin activity to less than 60% of normal occurred in 28 patients. Of these, 93% had evidence of liver disease or congestive heart failure, or both.

3. It is suggested that the response to a small test dose of dicumarol may be useful as an additional test of liver function.

The dicumarol used in this study was supplied in part by the Eli Lilly Co. The prothrombin times were performed by Mrs. Eva Roditi who also proved invaluable in many other ways.

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# A CLINICAL EVALUATION OF A NEW LIVER FUNCTION TEST, THE COLLOIDAL RED TEST, IN COMPARISON WITH THE THYMOL TURBIDITY TEST\*

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Ducci<sup>2</sup> recently reported a simplified modification of Maizels' colloidal red test<sup>10</sup> and claimed results fully as good as those obtained by MacLagan<sup>3</sup> with his modified colloidal gold reaction. Neefe *et al.* (in a footnote)<sup>11</sup> have substituted the colloidal red test for the colloidal gold test for the purpose of routine study in his laboratory. Accordingly, it was deemed advisable to undertake the following investigation:

1. A confirmation of Ducci's<sup>2</sup> and Neefe's<sup>11</sup> reports as to the value of the colloidal red test.

2. A comparison of the colloidal red and thymol turbidity tests on a large scale.

**Methods and Material.** The thymol turbidity test was performed as described by Ernst and Dotti<sup>3</sup> except for a slight change in the barium sulfate standard as suggested by Kunkel.<sup>5</sup> This change made only a slight difference in the unit readings not exceeding the experimental error in the method.

The colloidal red test was performed as described by Ducci<sup>2</sup>: 0.1 cc. of serum was added to 1 cc. of buffer solution, mixed, and 5 cc. of colloidal red solution was added and mixed. Results were read at the end of 24 hours. Readings were the same as those recommended by the author with the exception of his 1 plus interpretation. In this case we called the faintest precipitate visible without shaking a 1 plus reading. Each new batch of reagent was standardized by running known positive and negative sera in

duplicate with old and new reagent. At present we are investigating methods of standardizing the reagent colorimetrically in order to simplify the problem of its reproducibility.

The groups of subjects chosen for this study were comparable to those reported previously<sup>3</sup> and consisted of the resident population of the hospital, volunteer and professional blood donors, and patients. The blood donors were all presumably at least 4 hours fasting at the time of sampling. All other blood specimens were obtained in the fasting state. All grossly lipid sera were treated separately since Kunkel<sup>6</sup> and Shay *et al.*<sup>12</sup> have mentioned the possibility of lipid sera giving false positive thymol tests.

**Results and Discussion.** **NORMAL CASES.** Forty-two normal cases were selected from the resident population and from this group we obtained an average thymol value of 2.5 with a mean deviation of 1.6. Four of this group showed elevated thymol values for a 9% incidence. In this same group there were 2 positive colloidal red tests for an incidence of 5%. These 2 tests were rechecked in view of the fact that the thymol turbidity value in each case was normal. These values for thymol turbidity for normals are lower than the figures reported by Ernst and Dotti.<sup>3</sup> This is due to the fact that they included in their series of normals a large number of blood donors which

\* This study was aided in part by a grant from the Belleair Securities Corporation.

we will show give a higher thymol turbidity value than hospital personnel.

In a group of 228 blood donors the samples were divided into two groups: (1) 201 cases with clear serum and (2) 27 cases of grossly lipid serum. In group one the average thymol turbidity value was 3.4 units with a mean deviation of 2.4 units. There were 37 values above 5.0 units for an 18.5% incidence of positive tests. In this same group there were 9 positive colloidal red tests for an incidence of 4.5%. Of these 9 cases 7 also had positive thymol tests.

In separating these 2 groups now we find a lower incidence for our selected normals (9%) and a higher incidence

were obtained from this group alone necessitating separate treatment of these sera.

Of the 27 cases in Group 2, 17 (63%) gave positive thymols, while 3 (11%) gave positive colloidal red tests. Coincidentally these 3 cases all had positive thymol tests. The average thymol value in this group was 7.4 units with a mean deviation of 5.2 units. These results would seem to confirm the observations of Kunkel<sup>6</sup> and Shay *et al.*<sup>12</sup> that lipemia interferes with the thymol turbidity test. This may also be true of the colloidal red test so that both tests should be carried out on individuals in the fasting stage only.

TABLE 1.—COMPARISON OF THYMOL TURBIDITY TEST AND COLLOIDAL RED TEST IN PRIMARY HEPATIC DISEASE

Disease	Number Of Cases	Positive Thymol Turbidity	Positive Colloidal Red
Infectious Hepatitis	5	5	5
Post Infectious Hepatitis (1 year followup)	5	3	3
Laennec's Cirrhosis	10	9	7
Hepato-splenomegaly, unknown etiology	1	0	0
Chronic Alcoholism	4	4	1
	<hr/> 25	<hr/> 21	<hr/> 16

(18.5%) for the donor group than the previously reported 13% incidence for the combined group. In re-evaluating the donor group we learned that a number of so-called "professional" donors available to our blood bank consisted of chronic alcoholics whose medical histories were unreliable. For example, one such supposedly healthy donor had a thymol value of 21.9 units, a 4 plus Hanger, and a 4 plus colloidal red reaction. The possibility exists, therefore, that a number of these people may have some form of hepatic involvement and that this factor may play a part in the high incidence of positive tests in this group, especially those in whom both tests were positive. Inability to control the fasting state in donors may also be a major factor in this group. This is borne out by the fact that a large number of lipid sera

HOSPITAL CASES. In addition to diseases involving the liver primarily it is well established that many diseases can affect the liver secondarily.<sup>1,4,6,7,9,10</sup> Accordingly our hospital cases were divided into two groups:

(1) Patients without any known liver involvement (control group).

(2) Patients with known primary or possible secondary liver involvement.

There were 204 cases in Group 1, of which 25 (12.3%) gave positive thymol turbidity reactions. The average thymol turbidity value was 2.8 units with a mean deviation of 1.8 units. There were only 2 positive colloidal red tests in this group for an incidence of 1%. Both of these cases also had positive thymol tests and included one case of scleroderma and one case of Buerger's disease. The thymol turbidity values and the incidence of posi-

tive tests in this group are lower than those previously reported by Ernst and Dotti.<sup>3</sup> This may be explained by the fact that in the previous publication cases of secondary liver involvement were included in this group rather than being treated separately as in this paper.

It is apparent from the data presented that the colloidal red test has a low incidence of positive results in our control groups and in the great majority of these instances the thymol turbidity test was also positive. There

hepatic disease. Table 2 shows the results in diseases with possible secondary liver involvement. A summary of the positive individual cases is given in Table 3.

Our series of liver cases is admittedly too small to justify any conclusions at the present time. However, the limited data on liver disease does indicate several trends. It would seem that the colloidal red test correlates best with the thymol reaction in infectious diseases of the liver such as infectious hepatitis and infectious mononucleosis.

TABLE 2—COMPARISON OF THYMOL TURBIDITY TEST AND COLLOIDAL RED TEST IN DISEASES WITH POSSIBLE SECONDARY LIVER INVOLVEMENT

Disease	Number Of Cases	Positive Thymol Turbidity	Positive Colloidal Red
Cardiac Decompensation with Chronic Passive Congestion of Liver	7	5	3
Polycythemia Vera with Hepato-splenomegaly	1	1	1
Metastatic Carcinoma of Liver	2	1	0
Cholecystitis and/or Cholelithiasis	12	4	3
Subacute Bacterial Endocarditis	1	1	1
Infectious Mononucleosis	9	9	9
Bocck's Sarcoid	3	3	3
Rheumatoid Arthritis	3	3	2
Rheumatic Fever	3	1	1
Sickle Cell Anemia	1	1	1
Bronchopneumonia	15	5	4
	<hr/> 57	<hr/> 34	<hr/> 28

were only 4 instances in which the colloidal red test was positive and the thymol reaction was normal. Two of these occurred in the blood donor group and 2 in our normal control group. The significance of this is not clear at the present time. Especially satisfactory was the low incidence (1%) in our hospital control group where the collection of fasting samples could be rigidly controlled.

We have arbitrarily divided the cases in Group 2 into those with primary liver disease and those who might have liver involvement secondary to some other disease process. Table 1 shows the results of the colloidal red test as compared with the thymol turbidity test in primary

In other diseases of the liver such as metastatic carcinoma, compensated cirrhosis, and chronic alcoholism, liver function tests can be unreliable and misleading.<sup>11</sup> The seeming lack of correlation between the two tests in this group of diseases may therefore be more apparent than real. It would also appear that, in general, there is a quantitative relationship between the thymol and colloidal red tests in that the colloidal red test becomes more positive as the thymol value increases in units. Conversely as clinical improvement becomes apparent the values for both tests decrease accordingly.

We wish to emphasize at this point that this report is in the nature of a

preliminary one and is concerned primarily with the incidence of positive colloidal red tests in control groups. The value of any test, in part, is inversely proportional to the number of false positive tests obtained. The very low incidence of positive colloidal red tests in our control groups indicates the possible value of this test when considered from this point of view.

the colloidal red test in liver disease is being carried on at present and will be the subject of a future report.

Summary. 1. A comparative study of the thymol turbidity and colloidal red tests was made and the results discussed.

2. The low incidence of positive colloidal red tests in the normal and hospital control groups as opposed to

TABLE 3.—TABULATION OF INDIVIDUAL PRIMARY AND SECONDARY LIVER DISEASES

Diagnosis	Number of Cases		Values									
Infectious Hepatitis	5	TTV*	10.3	24.0	16.5	17.9	6.8					
		CRV**	1+	5+	3+	4+	1+					
Post Infectious Hepatitis (1 year follow-up)	3	TTV	7.2	5.6	6.4							
		CRV	3+	1+	1+							
Laennec's Cirrhosis	9	TTV	7.0	6.3	19.3	5.9	8.7	6.2	15.9	7.0	14.3	
		CRV	1+	1+	3+	0	0	1+	3+	3+	4+	
Chronic Alcoholism	4	TTV	9.7	7.7	8.3	9.0						
		CRV	1+	0	0	0						
Chronic Passive Congestion of Liver	5	TTV	10.4	18.0	12.7	6.1	7.0					
		CRV	3+	4+	1+	0	0					
Polycythemia Vera with Hepato-splenomegaly	1	TTV	8.0									
		CRV	1+									
Metastatic Carcinoma	1	TTV	5.2									
		CRV	0									
Sickle Cell Anemia	1	TTV	9.5									
		CRV	1+									
Bronchopneumonia	5	TTV	8.9	6.2	10.0	8.7	11.9					
		CRV	0	1+	2+	2+	1+					
Cholecystitis and/or Cholelithiasis	4	TTV	10.7	8.7	5.0	5.3						
		CRV	2+	1+	1+	0						
Subacute Bacterial Endocarditis	1	TTV	5.3									
		CRV	1+									
Infectious Mononucleosis	9	TTV	8.4	10.0	11.0	14.2	6.4	10.0	6.9	18.1	10.3	
		CRV	1+	2+	2+	2+	1+	1+	1+	3+	1+	
Boeck's Sarcoid	3	TTV	7.4	9.3	7.9							
		CRV	2+	1+	2+							
Rheumatoid Arthritis	3	TTV	11.5	8.4	5.5							
		CRV	3+	0	1+							
Rheumatic Fever	1	TTV	5.9									
		CRV	1+									

\* =Thymol Turbidity Value

\*\* =Colloidal Red Value

Conversely, with one or two exceptions, both tests correlate very well in our cases of known hepatic involvement. From our present data it would appear that the colloidal red test gives a very low incidence of false positive tests and a very high incidence of positive tests in hepatic involvement. More intensive investigation of the value of

the high incidence of positive thymol reactions in these same groups together with the seemingly good correlation of these tests in infectious liver diseases would seem to justify our present opinion that the colloidal red test is a valuable liver function test.

3. In view of our findings in the donor group of controls we deem it

advisable not to use such a group as normals in studies of liver function tests.

4. Our studies confirm the work of Ernst and Dotti insofar as a high incidence of positive thymol reactions existed in all of our control groups.

The lowest value obtained was 9% in a selected group of young healthy adults while our hospital group of controls gave an incidence of 12.3%.

5. The use of both tests as screening liver function tests has been valuable in our hands.

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# PROGRESS OF MEDICAL SCIENCE

## DERMATOLOGY AND SYPHILOLOGY

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## THE TREATMENT OF SCLERODERMA

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Two recent reviews in this journal, one on the visceral manifestations of scleroderma by Beerman<sup>3</sup> and the other on the radiological aspects of the same disease by Pugh<sup>34</sup> re-emphasize the far-reaching effects on the individual of generalized scleroderma. In a disease of such eventual widespread involvement, a knowledge of the potentialities of therapy in patients suffering either from the localized type of scleroderma (morphea) or the beginnings of the generalized form is to be desired. From a study of the literature and personal experience, it appears that treatment of scleroderma of various types is far from satisfactory. This dearth of effective therapeutic means is due in part to the gaps in our knowledge of the probable pathogenesis of scleroderma, and in part to the rarity of the disease. This latter circumstance precludes the pos-

sibility of large series of well-controlled cases. Accordingly, in this discussion we shall even "grasp at a straw" by citing on occasion the results of a particular treatment regimen in one or at most a few cases.

The value of physiotherapy and climatic treatment will not be evaluated in this review beyond the statement that in the management of generalized scleroderma certain physical means such as heat, massage and hydrotherapy may be helpful in some cases. Furthermore, change in climate may yield an advantage to some patients. In fact, in his survey of the Place of Health Resort Therapy in Dermatologic Disorders, Cipollaro<sup>10</sup> reaffirmed the prevalent idea that "certain vascular diseases such as Raynaud's disease, pernio (chilblains), sclerodactylia and scleroderma are benefited by climatic condi-



tions. Patients with these disorders do not tolerate cold weather well. At a health resort located in a warm climate and possessing adequate facilities for medical treatment, patients with vascular diseases can be made more comfortable and their life prolonged."

It is pertinent here to call attention to previous attempts to collect the available data for the treatment of scleroderma. Among these are the massive study of Boardman<sup>7</sup> and the relatively recent reports of Duryee<sup>14</sup> on Scleroderma, Modern Concepts of Therapy (1942), and of Dennie and Morgan<sup>12</sup> on the Treatment of Certain Types of Scleroderma. Other sources of therapeutic suggestions and results will be specifically mentioned in appropriate places. In assessing the value of any treatment procedure in scleroderma, the factor of spontaneous improvement must always be kept in mind.

As is the case with any disease for which no one mode of therapy is specific, there are innumerable procedures which, having given good results in someone's hands, are highly recommended. A list of "recommended" treatment is given in Table 1.

TABLE I. — PROCEDURES RECOMMENDED FOR TREATMENT OF VARIOUS TYPES OF SCLERODERMA.

1. *General Supportive Measures:*  
Treatment of underlying causes: syphilis; neurocirculatory instability, etc.
2. *Endocrine and Ferment Therapy:*  
Thyroid; pituitary extract; sex hormones all types. Ferment therapy (Sellei).
3. *Vitamins:* C, D, and E (?).
4. *Miscellaneous Medicaments:* Paraaminobenzoic acid; Promin; ammonium chloride (induced acidosis); Benadryl; heavy metals (gold; bismuth).
5. *Irradiation Therapy:* Thorium X; indirect Roentgen irradiation; Radium ointment; Grenz rays.

6. *Fever Therapy:* Typhoid, hot baths.
7. *Mecholyl.*
8. *Prostigmine.*
9. *Surgical Procedures:* Sympathectomy; parathyroidectomy.

**GENERAL SUPPORTIVE MEASURES:** Aside from the physiotherapeutic and climatic regimens, noted above, this category of treatment includes nutritious diet and vitamins (see below), attention to underlying disease and nervous factors. The influence of syphilis and its treatment in various types of patients with scleroderma has been known for a long time. Hutchinson in 1884 reported the case of a patient with probable sclerodactylia and syphilis. Boardman<sup>7</sup> concluded after a thorough review of the literature that one had to admit that a large number of the cases followed infections or toxic conditions and especially syphilis. The possibility of the coincidental occurrence of the two diseases in the same patient or the presence of false positive serological reactions to the tests for syphilis must constantly be considered. On the other hand, it is not possible to dismiss summarily the occurrence of a relatively large number of abnormalities including positive Wassermann tests in the cerebrospinal fluids of patients with scleroderma. One cannot, furthermore, assume a syphilitic cause for scleroderma because it has been demonstrated repeatedly that drugs and procedures useful in the therapy of syphilis (see below) may benefit patients suffering with scleroderma.

With regard to the psychoneurogenic component in scleroderma, Stokes, Beerman and Ingraham<sup>40</sup> found that surprisingly little attention has been given in recent years to this aspect of the background of the vasomotor neuroses. In fact, in their review the question is raised whether the psychic factors involved in scleroderma play a primary or secondary rôle. Becker<sup>1</sup> on the other hand, believes that: "The syndrome embracing Raynaud's disease

and scleroderma and some other types of scleroderma appear to be on a basis of neurocirculatory instability, with alternate spasm and dilatation of the superficial blood vessels. Thyroid substance, if given in sufficient amount, vascularizes the skin, often producing improvement, although no real deficiency of the thyroid gland can be shown to exist. Our idea relative to the therapy for the conditions discussed is somewhat the same as that expressed by Christian, writing in regard to functional cardiac disease: "Endocrine disturbances, sympathetic and vagus imbalance, perverted metabolism, have been offered in the way of explanation, and treatment based on these ideas has been advised. All of these seem very fanciful, and the majority of clinicians do not accept such as playing any significant causative rôle. It seems best to regard these patients as definitely subnormal in some respect, particularly in nervous stability, largely on a congenital or developmental basis. This idea gives a good key to an understanding of the limitations of treatment."

**ENDOCRINE THERAPY.** In Beerman's<sup>3</sup> review of the visceral manifestations of scleroderma, the subject of endocrine involvement was discussed and declared to be controversial and unappraised. Similarly, the use of endocrine products in treatment remains on a relatively empiric basis. The subject has been exhaustively reviewed by Castle,<sup>9</sup> Boardman,<sup>7</sup> Seale<sup>30</sup> and Ehrmann and Brünauer,<sup>16</sup> among others. In general there seems to be an impression that thyroid extract in small doses over long periods yields benefit. When this matter is more fully investigated it appears that the reputation of thyroid therapy in scleroderma rests on a rather insecure foundation. Although there has been a relatively large number of cases of scleroderma showing thyroid involvement, clinical results have been equivocal, sometimes good and on occasion actually the reverse (Atwater).

O'Leary and Nomland<sup>29</sup> gave thyroid gland extracts to patients in whom the basal metabolic rate was below the average. They used either thyroxine, 4 to 8 mg., or desiccated thyroid gland, 67 to 125 mg. The dosage of the drug was regulated to keep the basal metabolic rate between 0 and +10%. Although the simultaneous use of other treatment vitiated estimation of the results from the thyroid medication, they found the results from the various preparations of the thyroid gland disappointing in the group as a whole. In cases of hyperthyroidism, thyroidectomy was performed without apparent change in the scleroderma. Likewise the use of compound solution of iodine in cases of exophthalmic goitre caused improvement in the general symptoms but without effect on the scleroderma. They concluded that the value of thyroid gland extracts in the treatment of scleroderma is dependent not on the specific influence of the extract or the fact that the gland is manifesting hypofunction, but on the influence that the extracts exert on increasing the blood supply in the cutaneous vessels.

While a polyglandular deficiency has also been considered in the background of scleroderma, benefit may follow the use in a given case of a single endocrine product such as thyroid, adrenal or ovarian preparations. Oliver and Lerman<sup>31</sup> treated 10 patients with daily injections of 1 cc. posterior pituitary extract over a period of 15 to 30 days, followed by a rest period of one month. Control patients were given 1 cc. of pancreatic extract with negative results. The immediate effect of the posterior pituitary extract was marked pallor, lasting 10 to 15 minutes followed by a flushing of the skin of longer duration. All the patients complained of abdominal cramps associated with bowel movements. All 10 patients sustained improvement, permanent in some of them. The increase in erythema in or about the lesions in 3 cases of morphea indicated an increase

in the blood supply. This increased blood supply, rather than a substitute true endocrine replacement effect, may be the factor responsible for the improvement. Contrary to Oliver and Lerman's experience, O'Leary and Waisman<sup>30</sup> found that daily injections of posterior pituitary over a long period were of slight benefit in their patients with acrosclerosis.

Although Duryee<sup>14</sup> included the female sex hormones among the preferred methods of treatment the relatively scanty literature is far from enthusiastic. The similarities of generalized scleroderma and dermatomyositis (Dowling and Griffiths<sup>13</sup>) suggest that the recent work of Lamb, Lain, Keatty and Hellbaum<sup>24</sup> on steroid hormones might be extended to the problem of the therapy of scleroderma. These authors observed significant clinical improvement in 4 cases of dermatomyositis by the injection of testosterone propionate. Clinical improvement was accompanied with significantly increased ability to retain exogenous creatine, increased muscular strength and moderation of cutaneous lesions. Best results were obtained in the earlier cases before permanent vascular and muscular changes had occurred.

Sellei,<sup>37</sup> while championing the duality of scleroderma and acrosclerosis, has included scleroderma among the group of diseases he has called "dysfermentoses". This term is used to designate those diseases arising in various tissues as a result of abnormal enzyme action, such as by ferments produced in the skin, bone marrow, and nervous system. He advocated a so-called ferment therapy for them. Administration of fresh or dried pancreas, as well as other digestive ferments, has yielded improvement with actual softening and disappearance of the cutaneous induration. Again, best results are obtained in the earlier phases of the process before atrophy has taken place. It is also of little use in acrosclerosis. According

to this investigator, ferment therapy is based on a "chemical system" composed of enzymes, ascorbic acid and metallic catalysts. For best results it is necessary to have the enzymes and other preparations fresh, given continuously and for a long time. The ferments must be given about 1½ hours before meals. Sellei prescribed 150 to 200 gm. of raw pancreas (mixed with mayonnaise, or leafy green vegetables containing ascorbic acid or sweet peppers, tomatoes, cucumbers, or an anchovy spread, or mushrooms). The remaining meals are left to the choice of the patient. However, with every repast there must be taken 3 pancreatin tablets, ascorbic acid, and iron. After several weeks the raw pancreas is replaced by pancreatin tablets and still later by raw liver (200 to 300 gm. daily) prepared as was described for the pancreas.

Sellei's work has not received widespread confirmation. Urbach<sup>48</sup> has found it of interest and Becker and Obermayer<sup>2</sup> noted that the administration of raw pancreas was of value in 2 patients with generalized superficial scleroderma. However, O'Leary and Waisman<sup>30</sup> have not seen any impressive effects from the use of insulin-free extracts of pancreas or of other tissue extracts.

**VITAMINS.** A growing literature on scleroderma involves the use of vitamins in treatment. The data regarding vitamin D are convincing. Those involving the use of vitamin C and those indicating the possible value of vitamin E are highly conjectural.

Disturbance of calcium metabolism is consistently found in scleroderma. This is especially prominent when scleroderma occurs together with calcinosis, such as is the case in the so-called Thibierge-Weissenbach syndrome. Since there is evidence that scleroderma may in some way be related to hyperfunction of the parathyroid gland, and since the latter has a definite relationship to calcium metabolism, it is obvious that

this may be the basis for the disturbed calcium metabolism in this disease. Cornbleet and Struck<sup>11</sup> found that both calcium and phosphorus are retained in the body. This retention can be accounted for, for the most part, by the abnormally small quantities excreted in the urine. Large doses of viosterol markedly increase the calcium content of the urine and thereby produce a loss of calcium and phosphorus from the body. Cornbleet and Struck<sup>11</sup> offer an hypothesis to the effect that scleroderma is initially due to a toxin which injures the collagen syncytium and that the injured tissues secondarily take up calcium. This disposition of calcium may account for the frequently observed positive balance in scleroderma. As a result of this reasoning Cornbleet and Struck tried, with success, 200,000 to 300,000 international units of vitamin D daily in 11 cases of scleroderma. In 1939 Hummel<sup>22</sup> noted that AT-10 (dihydrotachysterol) was of use in scleroderma. At least 4 months of continuous treatment is required for improvement; and sclerodactylia responds more slowly than generalized scleroderma. Similarly Bernstein and Goldberger<sup>5</sup> found 1 cc. daily doses of dihydrotachysterol for 2 to 4 week periods until 75 cc. had been administered, of benefit in a 70 year old woman with scleroderma. There were no changes in the blood calcium or phosphorus values during treatment. Norman<sup>27</sup> also studied the effects of 50 to 100 thousand units a day of vitamin D on 3 women with scleroderma all of whom had Raynaud-like changes in the hands and feet. All sustained pronounced general improvement with restoration of the skin practically to normal and an increased joint mobility. There was depression of the ovarian function in all 3 patients, and relapse occurred after treatment was stopped. Duryee<sup>12</sup> felt that although his experience with dihydrotachysterol has not produced demonstrable improvement, it seemed to have some

beneficial effect on one case in which parathyroidectomy had been performed. Since dihydrotachysterol is a sterol, its effect on calcium metabolism may be similar to that of estrogens. He felt that further investigation of this product is warranted.

Although there is apparently no evidence for vitamin deficiency in scleroderma but because vitamin C has potentialities in promoting wound healing, Duryee makes vitamin C a part of his routine of therapy. Indications that vitamin E may have some merit in scleroderma are found in the influence of this preparation on vascular disease (Shute, Vogelsang, Skelton and Shute<sup>39</sup>). The recent report of Burgess and Pritchard<sup>8</sup> on the successful treatment of ulcers of the legs with vitamin E, and their use of it in lupus erythematosus seems to support the ability of the tocopherols to regenerate collagenous tissue.

**PARA-AMINOBENZOIC ACID.** In a preliminary statement, Zarafonitis<sup>47</sup> reported on the use of paraminobenzoic acid preparations in unspecified dosage in 5 patients with a wide range of sclerodermatous involvement. There was improvement in 4. It appears to be best in the most extensive cases. There is a gradual softening of the affected parts with an increased range of motion. This agent deserves further critical study because of its potential toxicity.

**PROMIN.** In a preliminary report Wuerthele<sup>15</sup> stated that she had reason to suspect a bacterial origin for scleroderma. On the supposition that this organism was a mycobacterium as in leprosy and tuberculosis, she treated a patient with scleroderma with promin in tragacanth jelly (sodium P,P'-diamino - diphenyl sulfone - N - N' didextrose sulfonate). The patient was able to return to work in 2 months. In a later paper<sup>16</sup> Wuerthele-Caspe and her co-workers reported the finding of an acid-fast bacillus in 5 cases of scleroderma (in sputum, blood, nasal and

subcutaneous tissue and has been grown from blood). All the patients treated with the promin locally, orally or by injection, showed definite, responsive changes. This work needs confirmation.

**AMMONIUM CHLORIDE IN THE TREATMENT OF SCLERODERMA.** In spite of Leriche and Jung's<sup>25</sup> feeling in favor of the operative (parathyroidectomy or sympathectomy) treatment of scleroderma, they did not venture to propose surgical treatment at the onset of 2 cases of scleroderma, and their patients passed through the gamut of medical treatment. In the 2 years preceding the date of publication they tried ammonium chloride which increases the elimination of calcium by way of the urine. They cite in detail a case of a woman with early scleroderma in plaques on the face which had resisted various medicaments and which continued to spread. Blood calcium was .103 gm. (hypercalcemia). She was placed on the following regimen designed to increase the elimination of calcium which Pautrier and his collaborators had shown was increased in scleroderma. 1, Acidifying regimen: Take bread, pastry, rice, sweetmeats, meat and fats. Avoid milk, green vegetables and fruits. 2, Ammonium chloride 3 gm. daily. After 20 days of this regimen there was a marked improvement in the skin and the blood calcium fell to 0.089. The patient lapsed treatment and while under thyroid extract at another physician's hands there was a relapse of the local and systemic complaints. Resumption of the ammonium chloride was followed by rapid improvement. Since that time on numerous occasions the symptoms recurred when the treatment was stopped. New lesions appeared even when thyroid-parathyroid extract was used. This makes the good effects of the ammonium chloride appear to be more than a coincidence. The same results were obtained with a second case of scleroderma (of the extremities). We have

personally seen similar results in several of our patients. The mode of action of the ammonium chloride is not definitely known. An acidifying regimen can double the urinary elimination of calcium. By the same mechanism, the acidosis produced by the large doses of ammonium chloride may considerably increase the excretion of calcium, may modify the pH and may produce an increase in the ionization of the calcium.

**BENADRYL.** O'Leary and Farber<sup>28</sup> have administered beta-dimethylaminoethyl benzhydryl etherhydrochloride (benadryl) to 9 patients who had acrosclerosis and to 4 who had scleroderma. The benadryl was given by mouth in amounts varying from 200 to 800 mg. a day. A chief complaint of the acrosclerotic patients was their inability to flex their fingers or to make a fist. During the first 2 weeks of therapy 7 of the 9 patients who had acrosclerosis were able, because of the rapid disappearance of edema from their hands, to bend their fingers and to make a fist, and there was a decrease in the cutaneous edema of 2 of the 4 patients who had scleroderma. Sustained benefit, however, was achieved for only 2 of the 9 patients who had acrosclerosis. Pyribenzamine and other antihistaminics may also yield similar results.

**HEAVY METAL THERAPY.** Although the coincidence of syphilis and scleroderma improved by anti-syphilitic therapy has been noted above, heavy metals (gold and bismuth) have exerted a non-specific beneficial effect in various types of scleroderma. Preinger,<sup>33</sup> for example, believing scleroderma to be an infectious process, used gold in the treatment of 3 cases of the diffuse type, 2 of the circumscribed variety, 2 of acrosclerosis and 1 of scleroderma. Treatment consisted of intramuscular injections of 0.01 to 0.05 and 0.1 gm. solganal B in children and 0.25 to 0.5 gm. in adults. The patients also received bismuth injections in conjunction with the gold. The treatment produced marked clinical improvement in

all patients except those with acrosclerosis. In the case of localized scleroderma, Flood and Stokes<sup>18</sup> taking the lead from 2 French reports<sup>34,38</sup> dealing with the successful treatment of this form of scleroderma with bismuth compounds, obtained excellent results in 2, good in 4 and fair in 1 case. Bismuth hydroxide ("Muthanol") and solution of sodium bismuth iodide and sodium iodide in propylene glycol containing saliginin and acetic acid (Iodobismitol) were used, but they noted that bismuth subsalicylate is also effective according to other reports. Recent use of oral bismuth preparations suggests the possibility of their wider application to the therapeutic regimen of scleroderma (Stryker *et al.*<sup>42</sup>).

**IRRADIATION METHODS OF THERAPY.** The use of thorium-X ointment in scleroderma was first recommended by Bloch.<sup>6</sup> In 1933 Epstein<sup>17</sup> obtained good results in all the patients he treated with this means, but best results were obtained in the circumscribed form of the disease. He employed an ointment of 1000 to 2000 electrostatic units in 1 gm. The ointment is applied on a wooden applicator to the affected areas, covered with gutta percha, bandaged and left in place for 18 to 48 hours, usually 24 hours. Treatments are given at 6 to 12 week intervals and as many as 10 treatments have on occasion been given to one area. No late sequelae had been observed after 15 years of trial in the Breslau Clinic.

Indirect roentgen irradiation therapy of the central and vegetative nervous system was found to be of some value in stopping the unfavorable progress of scleroderma by Foerster<sup>19</sup> and by Halter and Lundt.<sup>20</sup>

Strassburger<sup>11</sup> has suggested the use of Radon ointment for scleroderma. Grenz rays have also been used with benefit in a limited number of cases.<sup>21</sup>

**FEVER THERAPY.** Fever treatment with intravenous typhoid vaccine injected weekly for 10 to 20 weeks has

been tried with some success in acrosclerosis and diffuse scleroderma. Recently Dennie and Morgan<sup>12</sup> described the fever treatment of circumscribed scleroderma by means of hot water baths. In 1934 one of these investigators treated a case of central nervous system syphilis with hot water baths. This patient also had a large plaque of morphea on the back. Follow-up examinations revealed a startling regression of the sclerodermatous lesion and after a period of 6 months the sclerotic process had completely disappeared. There was only residual pigmentation where a purplish halo  $\frac{1}{2}$  of an inch wide had surrounded the original lesion with mild atrophy over the site of the plaque. This result encouraged the writers to regard hot baths as a promising therapeutic measure in scleroderma, since they felt that the vascular dilatation and resultant improved circulation must have been the main factor in overcoming the basic angiotrophoneurosis. However, it was also felt that through this medium of raising the body temperature, the reticulo-endothelial system would stimulate the body's natural defense mechanism. Thus if any toxic factors were present as etiological agents, the chances of their suppression should be enhanced.

Since this original experience, Dennie and Morgan have tried hot baths on several cases of scleroderma, including the generalized or diffuse types, as well as with acrosclerosis. Real success has been confined to circumscribed scleroderma of the plaque and linear types and morphea guttata. Up to the present they have had complete regression of these types of lesions in 3 cases over a 12 year period. In only 1 of these 3 cases, however, were hot baths the only attempted therapeutic measure. Glandular extracts from the ovary, thyroid, pituitary and pancreas and a concentrated vitamin A and D preparation were tried first but little or no success was noted until fever therapy by means of hot baths was instituted.

Dennie and Morgan's method of administering hot water baths can be utilized by the patient at his home, and thus is inexpensive and can be easily carried out. The only equipment necessary is a bath water thermometer, which can generally be purchased from any large dairy, a clinical thermometer, a bathtub with hot, running water, two cotton and two woolen blankets, bath towel and ice cap. An additional member of the family must render assistance at home for this method of therapy.

**MECHOLYL IONTOPHORESIS.** In 1937 Duryee and Wright<sup>15</sup> reported on their experience with methyl choline iontophoresis. Up to 1942 they had used it for 9 years and at least 50 patients had received this form of treatment. There was marked or moderate improvement in 60% of these cases. It is not a specific treatment but causes increased vascularity of the involved parts. Rittenbruch<sup>35</sup> found acetylcholin to act definitely on the mobility of the joints as well as on the skin diseases. O'Leary and Waisman<sup>30</sup> observed no outstanding results from the oral or hypodermic use of mecholyl chloride (acetyl beta methyl choline chloride) in acrosclerosis.

**PROSTIGMINE.** Based upon Perlow's<sup>32</sup> use of prostigmine in the treatment of peripheral circulatory disturbances, O'Leary and Waisman<sup>30</sup> found the oral use of the bromide or the methyl sulfate subcutaneously of some value in the treatment of their patients with acrosclerosis.

**SURGICAL THERAPY OF SCLERODERMA.** Since Leriche proposed the treatment

of scleroderma surgically by an interruption of the function of the sympathetic nervous system, a large group of investigators have treated a varying number of patients by this method with good or indifferent results. The literature on this surgical approach to the problem of scleroderma has been carefully collected by Hämäläinen and Söderlund,<sup>21</sup> to which paper the reader is referred. All agree that there is immediate improvement of variable degree but the final results leave much to be desired. Duryee<sup>14</sup> has summarized his views against sympathectomy as follows: "1, In those cases referred to our clinic in which this procedure has been carried out, no permanent improvement was noted. 2, The nature of the cutaneous lesions would prevent an increase in the vascular supply in the involved area even if the element of spasm were removed (Printzmetal). 3, The spasm which is present may occur independently of the nerve supply (Lewis). 4, In the majority of the patients the affected vessels are generalized (*not confined to those affected by the sympathectomy*. Eds.). 5, The improvement in vasodilatation is usually temporary (Johnson and Berheim and Garlock)."

Parathyroidectomy<sup>4,26</sup> merely influences one factor, the calcium metabolism in scleroderma. Some investigators have reported good early and late results and others have found this procedure wanting.

On the whole, in view of the indifferent results from surgery at the hands of conservative authorities, surgical methods should be the last resort in scleroderma of all types.

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# OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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## THE OVERMEDICATED NASAL CAVITY

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NASAL vasoconstrictors are among the most important drugs available to rhinologists. The weight of evidence indicates that these drugs afford symptomatic relief only and are not curative. Nasal vasoconstrictors can relieve nasal congestion for varying periods of time and when judiciously employed aid in promoting adequate drainage from the paranasal sinuses. Even temporary relief from the discomfiture of nasal obstruction is a boon to the individual so afflicted, and a number of sympathomimetic amines have come to assume a legitimate place in the therapeutic armamentarium.

Animal experimentation as a basis for observing the histophysiologic effect on nasal mucous membrane of various nasal preparations is well recognized, but not always practiced. Although it is obviously advisable to determine the histophysiologic effect of drugs on the normal nasal mucous membranes of experimental animals before advocating their widespread use in human beings, knowledge of undesirable caustic reactions sometimes comes initially via the patient's nasal cavity.<sup>1a</sup> If the truth be stated bluntly, this is literally paying through the nose. Years after its position in rhinology had been liquidated by clinical trial-and-error, it was learned, for example that when mercurochrome is introduced into the nasal cavities of experimental animals, the substance will pass through the mucous membranes of the

nasal cavity and paranasal sinuses, through the turbinates, through the bony walls of the frontal sinus, and even through the dura, to discolor the cortex of the brain in much less than 2 hours!<sup>1b</sup>

Experiences of the past decade have demonstrated that it is possible to curtail greatly, if not completely, two man-induced sequelae to promiscuous nasal medication — lipoid pneumonia and argyrosis. Recognition of the shortcomings of mineral oil as a vehicle for nasal medicaments, and its subsequent omission in numerous preparations, in all probability have diminished the incidence of lipoid pneumonia from this source. On the other hand, if one were to propose an aphorism to describe the overmedicated cavity, it would run something like this: over-treatment can sometimes prove just as damaging as the absence of treatment. It is known, for instance, that argyrosis of the nasal mucous membranes can be due to prolonged administration of silver salts in direct contact with the nasal mucous membranes. Bryant<sup>1</sup> found silver deposits in the biopsy specimens of nasal tissues of rabbits after having instilled various silver salt preparations intranasally for a period of 8 weeks. He maintains that the promiscuous use of silver-containing nasal medicaments is dangerous and accomplishes nothing that cannot be accomplished safely and more efficiently by other means.

According to Kully,<sup>8</sup> the action of sympathomimetic amines is chiefly on the blood vessels, although the secretory function is also involved. The subepithelial capillaries, the arterioles and the venous sinuses of erectile tissues are subject to constriction, and nasal secretion is diminished. If vasoconstriction is severe or prolonged, a secondary vasodilatation ensues, involving the deeper venous sinuses more than the subepithelial vasculature and leaving the mucous membranes blanched. Occasionally, the secondary reaction may be more evident and prolonged than the primary constriction. Secondary vasodilatation is influenced chiefly by the type and amount of the drug used and by sensitivity of the vasomotor mechanism.

In individuals in whom sensitivity to nasal vasoconstrictors has been established, Wright<sup>18</sup> declares that the predominant complaint is nasal stuffiness. The patient who overmedicates his nasal cavity usually does so to relieve a sensation of congestion. Usually the underlying condition is an acute cold or a recurrent attack of chronic sinusitis. The use of nose drops may have been initiated on the patient's own responsibility or in some instances on the advice of physicians. As the practice of frequent intranasal medication continues over prolonged periods of time, the relief becomes less pronounced; finally, little or no relief is obtained. Clinically, the mucous membranes of the overmedicated nasal cavity are often indistinguishable from tissues seen during acute allergic episodes. In Wright's<sup>18</sup> experience all the patients with nasal sensitivity to a nasal vasoconstrictor have employed synthetic preparations and not natural ephedrine products. In general, many synthetic products provide a greater degree of vasoconstriction and a more prolonged effect than ephedrine.

Excessive use of sympathomimetic amines for a prolonged period of time

can cause a clinical syndrome appropriately termed "vasomotor rhinitis medicamentosa." Fortunately, nasal sensitivity to vasoconstrictors can be checked rapidly by discontinuing the offending medicament. Vasomotor rhinitis medicamentosa, like lipoid pneumonia and argyrosis, is man-induced; its saving grace is the promptness with which cures can be established. No rational employment of nasal medication will countenance deliberate and promiscuous overindulgence.

Ryan<sup>12</sup> undertook a study to observe the histologic changes in the nasal mucous membranes of rabbits produced by the overuse of 2 types of nose drops. The first preparation was a 0.125% solution of dl-desoxyephedrine hydrochloride in a stabilized aqueous vehicle, 1.25% of anhydrous sulfathiazole sodium and 1.25% of sulfadiazine sodium; the second preparation was a solution of naphazoline hydrochloride (privine hydrochloride). Each of these preparations destroyed the cilia and the epithelium was transformed into stratified squamous epithelium. The subepithelial layer underwent fibrosis. The blood vessels became dilated and remained dilated for several weeks. Constriction and sclerosis of the blood vessels was observed at a later date.

The effects of prolonged medication with nose drops, nasal sprays and nasal inhalers of vasoconstrictor amines were studied in normal adult rabbits by Butler and Ivy.<sup>2</sup> The studies revealed that volatile inhalers and nasal sprays are similar in intensity and duration of effects produced, while nose drops appear less effective as a method of medication. The effects on the nasal mucous membrane produced by repeated administration of inhalers and sprays are similar, and both produced less pathologic change than that resulting from the use of nose drops. It seemed to the investigators that the selection of methods of medication in acute rhinologic conditions should be limited to

nasal inhalers and sprays in most instances. When it is desirable to direct medication to a specific area in the nasal chamber, such as the ostium of a paranasal sinus, nose drops may be the method of choice. In conditions requiring prolonged and repeated medication, sprays or inhalers are proposed methods of choice. In commenting on this investigation, it may be pointed out that clinical deductions were made from histologic study of the mucous membranes overlying the nasal septum. In actual practice, the purpose of liquid nasal medication as well as other means of intranasal medication is to shrink the mucous membranes of the turbinates in order to obtain relief rather than to constrict the mucous membranes overlying the nasal septum.

Various authors have called attention to the secondary congestion arising from use or misuse of *privine* hydrochloride. In general, the collective experiences appear to have been closely parallel. *Feinberg* and *Friedlaender*<sup>5</sup> comment on more than 75 individuals in whom symptoms of nasal congestion were aggravated or prolonged by the continued use of the vasoconstrictor; *Schiller*<sup>14</sup> describes the secondary congestion arising from the drug in seasonal hay fever; *Gollom*<sup>6</sup> writes about persistent nasal congestion following the use of the medicament; *Mertins*<sup>10</sup> discusses 3 cases of rhinitis medicamentosa from excessive self medication; and *Putnam* and *Herwick*<sup>11</sup> report a case of naphazoline hydrochloride dependence of 23 months duration. *Talmage*<sup>17</sup> describes the case of a 62 year old woman complaining of continuous nasal blockage. The patient had been using an 0.1% solution of *privine* hydrochloride for more than a year, employing more than 1 ounce of the medicament each week. Her dependence on the drug subsided completely within 3 weeks after its discontinuance.

*House* and *Carey*<sup>7</sup> call attention to the fact that children may exhibit a

different response to *ephedrine* and *privine* hydrochloride than that of adults, with sedation following a period of  $\frac{1}{2}$  to  $1\frac{1}{2}$  hours of mild stimulation. The systemic effects that may follow administration of the latter drug to children include prolonged hypertension with peripheral vasoconstriction; mild cortical stimulation, followed by depression; depression of the basal centers; and an ability to resemble and potentiate the action of the barbitals in depression of respiration. In this connection, *Childrey* and *Essex*<sup>3</sup> point out that absorption from the mucous membranes of the nasal cavity and paranasal sinuses is much more rapid when these membranes are inflamed. This may offer one explanation for an occasional case of systemic reactions. There is, in addition, also the possibility of sensitivity or idiosyncrasy to nasal medicaments.

That *ephedrine* and other types of nasal vasoconstrictors can cause secondary congestion is alluded to by *Scarano*<sup>12</sup> who observed the secondary reactions (returgescence, atony and bogginess) following frequent daily intranasal instillations of *ephedrine* and *amphetamine* in oil. Varying degrees of secondary reactions were noted in 5 of 25 individuals utilizing *ephedrine*, while reactions from *amphetamine* were virtually negligible. During a period of 6 years *Sternberg*<sup>16</sup> followed 32 patients whose nasal discharge and obstruction were due more to the continuous use of vasoconstrictors than to the underlying allergic condition. Eleven vasoconstrictors were employed and he observed no evidence as to which one produced more damage.

*Sevdell* and *McKnight*<sup>15</sup> write about 8 individuals with distressing disturbances to the olfactory sense which, they are convinced, are attributable to the intranasal instillation of 2 different preparations of *tyrothricin*, both, however, containing *tyrothricin* in concentrations of approximately 1:5000. The

solutions were applied by spray and as nose drops. Anosmia or parosmia developed after a solution of tyrothricin was used in the nasal cavity. These symptoms have been persistent, ranging in duration from 4 to 8 months. The symptoms have outlasted by months the condition for which the solutions were originally prescribed. At the time of the report none of the patients had regained a normal sense of smell. Most of the patients thought there had been some improvement, at least as far as intensity of parosmia was concerned.

The problem of producing new sympathomimetic amines is of great importance and deserves more attention in the pharmaceutical world. Until pharmacologists happen upon an abuse-proof type of liquid nasal medicament, in Fabricant's<sup>4b</sup> opinion, improved medicine droppers, among

other measures, are urgently required to assist patients in clinical utilization of controlled amounts of nose drops. The case for controlled dosage could be assured by the manufacture of a medicine dropper that would permit automatically a desirable number of nose drops to be released when instilling liquid nasal medication. A truly effective medicine dropper would go a long way toward abolishing some of the tendency toward uncontrolled overdosage and would assist materially in eradicating the fear of producing unpleasant side-reactions through overdosage. Perhaps the need for an ideal sympathomimetic amine will be answered at some future date—but until then specific measures for overcoming the abuse and misuse of liquid nasal medication through overdosage are required.

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PHYSIOLOGY  
PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF JANUARY 18, 1949

**Neuronal Changes Associated With Tetany of Alkalosis and Hypocalcemia.** HAROLD KOENIG, M.D., M.S., PH.D., and RUTH KOENIG, M.B. (Dept. of Anatomy, School of Medicine, Univ. of Penna.). These studies were carried out to test the hypothesis that the basophilic component of Nissl substance in the cytoplasm of neurons serves as a source of energy for neural activity and may be depleted if this activity is sufficiently great and prolonged.

Tetany greatly augments neural activity by producing repetitive spontaneous discharges both in motor and in sensory neurons, and probably also in interneurons. Hypocalcemic tetany was produced by intravenous administration of sodium citrate solution in one cat, and of a solution of mono- and dibasic sodium phosphate at pH 7.4 in another cat. Alkalotic tetany was produced by intravenous administration of a solution of sodium bicarbonate in 2 cats. Blood pH rose from 7.4 to 7.8-7.9. All 4 animals were kept in a severely tetanic state for 2 hours and then fixed by perfusion of the vascular system along with 2 normal control cats.<sup>1</sup> The brain and cervical enlargement of the spinal cord were stained with thionin<sup>2</sup>.

The large motor neurons of the spinal cord and brain stem were studied. In hypocalcemic tetany, these cells for the most part stained more lightly. The Nissl bodies were less sharp, lighter and fragmented as compared with the control sections. In alkalotic tetany, these cells were distinctly darker than comparable cells in control sections. The Nissl bodies were less sharp, but darker and often larger, and the cytoplasmic background showed a greatly increased basophilia.

The results obtained in hypocalcemic tetany are consistent with the energy theory of the function of Nissl substance. Alkalotic tetany, however, resulted in an increase of cytoplasmic basophilia. It is suggested that anoxia resulting from cerebral vasospasm produced by alkalosis, or the effect of the pH shift on intracellular enzymes involved in Nissl body metabolism, or both, are responsible for these changes.

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**Effects of Ablation of Cerebellar Cortical Tactile Areas in the Cat.** W. W. CHAMBERS, PH.D., and C. N. LIU. (Dept. of Anatomy, School of Medicine, Univ. of Penna.). Ablations of discrete portions of the anterior lobe of the cerebellum which are situated laterally to the vermal veins and coincide with the tactile receiving areas<sup>1</sup> have been performed. These areas are the tactile areas for the fore and hind foot.

Destruction of the fore and hind foot areas resulted in an ipsilateral loss of tactile placing reactions, overstepping of the ipsilateral limbs and reductions of hopping reactions. These symptoms have persisted for as long as 8 months.

Similar symptoms follow destructions of either the fore foot or hind foot tactile area but involve only the limb which corresponds to foot area removed (i.e., ablation of fore foot tactile area results in symptoms limited to the ipsilateral fore leg.)

That these changes in the postural reflexes, especially the enduring loss of the tactile placing reactions, may be due to increased postural tone is

unlikely, for the increase in postural tone in the affected limbs was minor as compared to the increased tone associated with medial vermal and, or, fastigial nuclear lesions, which are unaccompanied by loss of tactile placing reactions. Further evidence for the discrete symptomatology of the tactile area of the anterior lobe was obtained by ablations of nearly all parts of the medial vermis and cerebellar hemispheres without any impairment of placing reactions.

I. SNIDER, R. S., and STOWELL, A.: *J. Neurophysiol.*, 7, 331, 1944.

**The Functional Significance of some Thalamo-cortical Mechanisms.** HERBERT H. JASPER, M.D. (Montreal Neurological Inst., McGill Univ.) (By invitation.) The results of 2 types of experiment on the thalamus are recorded: 1, analysis of various local thalamic structures by stimulation of not more than 1 c. mm. of carefully located areas in the thalamus using the Clark stereotaxic instrument and recording the activity from over the cerebral cortex; 2, implantation of stimulating electrodes in different parts of the thalamus and observing subsequently the changes in behavior as recorded by cinematography following stimulation of various portions of the thalamus in the unanesthetized freely moving animal.

The results of the first series of experiments reveal 2 types of thalamo-cortical organization: *a*, the local nuclear cortical system, which involves a point to point projection from the relay nuclei to the sensory areas of the cortex and from the association nuclei such as the pulvinar and the dorso-medial nucleus to other cortical areas. This local point to point projection seems to be just as precise for the dorso-medial nucleus, for example, to various portions of the frontal lobe, as

is the localization of ventralis postero-lateralis to the postcentral gyrus. Overlapping this local system, there is, *b*, a diffusely projecting system, which we have called the *thalamic reticular system* which includes the intralaminar fibres and nuclei and the reticular nucleus. In the central core of this reticular system, which in the cat occupies the rostral portion of the massa intermedia, it is possible to stimulate over an area of not more than 2 to 3 sq. mm. in size and obtain control of spontaneous rhythmic activity of the entire cortex. This control is maintained even after destruction of the thalamic nucleus which projects in a local manner to this same cortical area so that it is an overlapping though diffuse projection system with particular functions, we believe, in the general regulation of excitability and possibly timing of events in various areas of the cortex relative to each other. From a portion of this system, it was possible to obtain the bilaterally synchronous wave and spike discharge very comparable to that seen in petit mal epilepsy.

The stimulation of this system in the unanesthetized animal with implanted electrodes reproduced a form of seizure, during a period after the end of stimulation, which simulated as closely as could be expected the petit mal lapse of responsiveness, without convulsive movements. With higher frequency and higher intensity stimulation of the same area, generalized major convulsive seizures were produced.

It was postulated that this thalamic reticular system which has its overlapping diffuse but yet topographically organized projection to all cortical regions must have some general facilitatory and possibly also inhibitory effect on cortical activity, perhaps homologous with the functions recently described by Magoun and Rhines for the bulbar reticular system.

# BOOK REVIEWS AND NOTICES

ADVANCES IN MILITARY MEDICINE. Edited by E. C. ANDRUS, D. W. BRONK, G. A. CARDEN, JR., C. S. KEEFER, J. S. LOCKWOOD, J. T. WEARN, M. C. WINTERNITZ. Assoc. Editor, TUCKERMAN DAY. Foreword by A. N. RICHARDS. 2 volumes. Pp. 965; 94 ills. Boston: Little, Brown, 1948. Price, \$12.50.

THE Office of Scientific Research and Development (OSRD) was Democracy's way to mobilize and correlate the nation's scientific resources in brains and equipment to meet the threat of totalitarianism during World War II. This 2-volume work deals with the activities of one of the subdivisions of OSRD: The Committee for Medical Research. By pooling their available basic information on topics germane to military needs and by assigning themselves the several angles of experiments to convert that information into practical uses, the medical scientists (nearly 1700 doctors and 3800 other trained investigators) were able to bring the methods of mass production and the assembly line to bear on the problems of military medicine and so to achieve, in a short time, results that might have been delayed for decades. (It must be pointed out that first steps, or the discovery of basic information, are overwhelmingly the work of the individual scientific "prospector", and are not amenable to mass-production methods.)

The material of these volumes is grouped according to the 6 subdivisions of the Committee: medicine, surgery, physiology, chemistry, aviation medicine, and malaria, with additional sections on penicillin and on sensory devices to aid the blinded. The 54 chapters are written each by a recognized authority on and participant in the particular phase of investigation, and represent the essential facts as set forth in about 1300 publications (whose references are an appendix of the work). The importance and manifold interest of the volumes are attested by such chapter headings as The prevention of infection in accidental wounds; The application of penicillin to surgical problems; New surgical plastics and hemostatics; The study of crash injuries and prevention of aircraft accidents; Motion sickness; The history of plasma fractionation; blood substitutes; Methods of preservation of whole blood; The development of new insecticides; New insect repellants; New rodenticides; The clinical testing of antimalarial drugs; Research in the development of penicillin. The manner of presentation is in

simple terms so that non-medical scientists will find it easy reading.

This publication is not merely the history of advances in military medicine: it is a record of brilliant achievement for all phases of medical practice. Every physician should read it with profit as well as interest and pride in his profession.

R. K.

HOSPITAL TRENDS AND DEVELOPMENTS, 1940-1946. Edited by A. C. BACHMEYER, M.D., Univ. of Chicago, and GERHARD HARTMAN, Ph.D., Univ. of Iowa. Pp. 819; New York: Commonwealth Fund, 1948. Price, \$5.50.

THE material used in this new book has been carefully selected from countless articles written during this period on the numerous phases of activities connected directly or indirectly with the development of the modern hospital. The editors, who are well known in the field of hospital administration and teaching, have gathered these articles into one volume in order that people interested in the hospital field may have access to recent writings by qualified people on the various subjects without undue reading of all the literature that has been published.

This is a companion to their earlier volume, THE HOSPITAL IN MODERN SOCIETY, which was published in 1940.

R. B.

ORAL AND DENTAL DISEASES. By HUBERT H. STONES, M.D., Prof. of Dental Surgery, Univ. of Liverpool. Pp. 896; 926 ills., many in color. Balt.: Williams & Wilkins, 1948. Price, \$18.00.

THIS is an excellent book. While designed particularly to meet the needs of dental students in the subjects of Oral Pathology and Oral Surgery it may also be recommended as a reference book for practitioners of medicine and dentistry. Oral lesions which are manifestations of systemic origin as well as those of local origin are considered in detail. Clinical features are fully described and illustrated with excellent photographs, many of which are in color. There are short but precise sections on treatment. Emphasis, however, is laid on etiology and histopathology and the many photomicrographs are well chosen and add considerably to the usefulness of the text. Recent research is cited frequently and its bearing on disease in the mouth competently discussed. The book gives evidence of the author's great experience in teaching and in examining students in various universities as

well as personal experience in investigative work.

It is difficult to select outstanding chapters for comment. Those on endocrine disturbances and nutritional deficiencies discuss experimental work and its relation to clinical diseases and malocclusion of the jaws and teeth are well treated. There are four chapters on stomatitis and allied diseases of the oral mucosa. The chapter on tumors is comprehensive and well illustrated. There is no mention, however, of fibrous dysplasia of bone which is now recognized as an important lesion occurring in the jaws and one which must be differentiated from neoplasms.

P. B.

**OCCUPATIONAL MARKS.** By FRANCESCO RONCHESI, M.D., Boston Univ. School of Med.; Pp. 181; 163 Ills. New York: Grune & Stratton, 1948. Price, \$5.50.

This brief volume is a tribute to its author. It emphasizes the place the objective dermatologic method of "look first and ask afterward" should have in the general scheme of medicine and specifically in personal identification. Dr. Ronchese has made a hobby "pay off" by producing within 181 pages a well-documented, excellently-illustrated compendium of occupational marks. While many of these data are available in scattered sources (adequately given in the bibliography), this is the most accessible compilation in English for the interested reader.

Included in this guide are certain general aspects of the subject such as specific occupational markings; professional markings; body areas and distinctive markings; deceptive markings and legal problems and classification of markings.

Although this volume is unique in many ways, its usefulness, in spite of the table of contents and index, could be enhanced by the addition of several lists with appropriate text and figure references, such as, for example, a list of marks and the particular occupations commonly yielding them, and a list of occupations with the marks produced by them.

H. B.

**TAKE OFF YOUR MASK.** By LUDWIG EIDELBERG, M.D., New York Psychoanalytic Institute. Pp. 230. New York: International Universities Press, 1948. Price, \$3.25.

This unusual book offers an account of psycho-analytic procedures to physicians and laymen. The author, a member of the Vienna, British and American Psychoanalytic Societies, has a remarkable ability to condense his stories and to make them interesting. His book of 8 chapters and 8 cases will richly repay its readers.

E. B.

**PSYCHIATRY.** By WILLIAM A. O'CONNOR, L.M.S.S.A. (Lond.). Pp. 380. Balt.: Williams & Wilkins, 1948. Price, \$9.00.

In this "short treatise" based on hospital and teaching experience in England, the author gives clinical descriptions of the neuroses and psychoses which are eclectic and conventional. In general he favors a psycho-analytic explanation of pathology. But in the discussion of wide principles he goes far to the left as he apparently reacts against mechanistic ideas prevalent in Britain and comes near suggesting that the real origin of all illness is in the mind.

E. B.

**MEDULLARY NAILING OF KÜNTSCHER.** By LORENZ BÖHLER, M.D., Prof of Surgery, TRETTER, M.D. Pp. 386; 1261 ill. Balt.: Williams & Wilkins, 1948. Price, \$7.00.

Univ. of Vienna. Translated by HANS

INTRAMEDULLARY nailing for fractures of long bones, introduced by Küntschner of Germany in 1940, has been used extensively in Europe. Until now, however, the method has been rarely employed in the United States. A comprehensive critique of the method by Lorenz Böhrer, a leading authority on fractures, is timely.

He analyzes experiences with intramedullary nailing in 600 fractures, emphasizing the narrow limits within which the method should be applied. Although he believes that intramedullary nailing is the best method available for the treatment of femoral shaft fractures which are not comminuted, he has discarded its use for the treatment of almost all fractures of the tibia, humerus, and forearm bones because of the frequency of complications.

Like most of Böhrer's writing the book is didactic in tone. It could have been profitably shortened if similar details of technique had not been repeated for each bone. American surgeons will be surprised by the frequent neglect of the patient's general condition and the failure to use proper supportive treatment during operation. The illustrations are profuse and wisely selected. Instructions in the actual technique of nailing are detailed and lucid. Surgeons of this country are indebted to Böhrer for furnishing this critical analysis of a valuable method of fracture treatment when experience here is as yet limited.

W. F.

**DIAGNOSIS IN DAILY PRACTICE.** By BENJAMIN V. WHITE, M.D., Ass't Clinical Prof. of Medicine, Yale Univ., and CHARLES F. GENSCHICKTER, M.D., Prof. of Pathology, Georgetown Univ. Pp. 693; 360 ill. Phila.: J. B. Lippincott, 1947. Price, \$15.00.



This book is not offered as a detailed textbook of medicine. It is intended as a guide for the advanced student, the intern, and the practitioner "In the selection of a daily routine which will embrace the more important and comprehensive diagnostic procedures" proven to be of value in the diagnosis of disease in its earliest stages.

The book is divided into 5 parts. The first of these (Chapters 1 to 3) defines the major human diseases as determined by morbidity and mortality statistical studies and gives the etiological classification and regional distribution of these diseases in the body. Lastly a routine diagnostic survey, utilizing procedures of known value in the diagnosis of the major diseases, is formulated. Part II (Chapters 4 to 12) is devoted to a discussion of the important symptoms occurring in the presence of the major diseases. Part III (Chapters 13 to 20) similarly deals with abnormal physical findings, and Part IV (Chapters 21 to 26) discusses laboratory procedures of use in diagnosing the major diseases. In each of these Parts are given differential diagnostic lists pertinent to the subject matter discussed therein. Part V (Chapters 27 to 49) presents the clinical features of the major diseases, with tables giving their differential diagnosis.

The authors can be commended for their practical and unique approach to an old and difficult problem. To this extent physicians will find this book of interest, but otherwise they are likely to find in it little that has not already been presented just as well or better elsewhere.

The publisher can be commended for presenting a book that is well bound and well printed on high quality paper. Illustrations, graphs, and tables are adequate and well done but there are a goodly number of typographical errors in the text.

R. K.

**HEMATOLOGY.** By CYRUS C. STURGIS, M.D., Prof. of Internal Medicine, Univ. of Michigan Medical School. Pp. 915; 72 ills. Springfield, Ill.: Charles C Thomas, 1948. Price \$12.50.

THIS volume, of imposing size and format, contains a good many typographical errors. Some of the colored plates are not informative. There is considerable redundancy of discussion. Some personal case reports might well have been omitted. A few strictly up-to-date topics, for whatever they may be worth, are missing from the index, such as: hypersplenism, hyperheparinemia, mast cells, the use of protamine and toluidin blue, "L.E." cells, cryoglobulins, auto-agglutinins, cold agglutinins, folic acid "antagonists", urethane, nitrogen mustard, "B-12", and "sludged blood".

Despite these adverse criticisms, the reviewer treasures this fine, scholarly clinician's summing up of his hematological wisdom in

the 23 chapters of this worth while book. Particularly valuable are the splendid paragraphs of history which introduce each major topic. For these as well as for the generally excellent, wise, authoritative clinical discussions of all important hematological subjects, the book is cordially recommended to students, practitioners, and specialists in the field. Although space-consuming, the duplication of bibliographic references, at the bottom of the pages as well as at the end of the book, is an innovation which is helpful and useful.

T. F-H., Jr.

**PATHOLOGY.** Edited by W. A. D. ANDERSON, M.A., M.D., F.A.C.P., Professor of Pathology and Bacteriology, Marquette Univ. School of Medicine. Pp. 1453; 1183 ills., 10 color plates. St. Louis: C. V. Mosby, 1948. Price, \$15.00.

THIS book is one of the most outstanding single texts on pathology which has been published in recent years. While the subjects of the chapters run the usual gamut of general and special pathology, often fine detail and recent research advances are included with the general information. The chapters are presented by different authors, many of them being leading investigators in their field, and consequently the text has more authority and fewer mistakes than most textbooks of pathology. The index is not complete, as occasional references are omitted. The book is replete with excellent illustrations. With the enormous amount of information contained within the 1400 odd pages, this text may be used with profit either for reference or for student teaching.

I. Z.

**THE PRACTICE OF ENDOCRINOLOGY.** By RAYMOND GREENE, M.A., D.M., and 6 collaborators. Pp. 366; 53 ills. London: Eyre & Spottiswoode, 1948. Price, \$10.60.

THIS book, planned for the general practitioner, essays to encompass the entire field of endocrinology in 10 chapters, with chief attention to diagnosis and treatment and little emphasis on physiology and pathology. As is usual, considerable variation in style and quality results from the collaborative effort. Though completed in 1946, the book's appearance was so delayed that a number of important recent advances are not included.

Some of the terminology will be a little strange to American readers. A number of subjects are either ignored completely or treated inadequately (e.g. hypogonadism in the male, ovarian deficiency with dwarfism, the relation of the parathyroids to renal disease, toxic nodular goiter, malignant tumors of the thyroid, the use of radioactive iodine). This book is not a major contribution to endocrinology, but may be a useful guide for the general practitioner.

E. R.

**ESSENTIALS OF PATHOLOGY.** By LAWRENCE W. SMITH, M.D., and EDWIN S. GAULT, M.D., Temple Univ. School of Medicine. 3d ed. Pp. 764; 740 ills., many in color. Phila.: Blakiston, 1948. Price, \$12.00.

In this standard textbook, first published in 1938, the general method of presentation has not been changed but numerous improvements have been made. The text has been completely reset, revised, and augmented. Reduction of the page size and of the number of pages has made the book much lighter and easier to handle. Space has been saved by condensing the case histories and eliminating blank spaces intended for students' notes. The high quality of the illustrations has been maintained by the addition of 61 new figures. As a text for students it can be well recommended. W. S.

**THE CLINICAL APPRENTICE: A GUIDE FOR STUDENTS OF MEDICINE.** By JOHN M. NAISH, M.D., M.R.C.P., and JOHN APLEY, M.D., M.R.C.P., Bristol Univ. Pp. 200; 71 ills. Balt.: Williams & Wilkins, 1948. Price, \$4.50.

Delightfully written in that inimitable English style, this small volume on physical examination and diagnosis should be required reading for all medical students. The material is succinctly and interestingly presented. The first section is concerned with the "leisurely examination", the second with the unconscious patient. Emphasis is placed upon the proper technique of examination. The book merits our unqualified approval. The price seems high and may restrict its widespread use. G. R.

**EXPERIMENTAL IMMUNOCHEMISTRY.** By ELVIN A. KABAT, Ph.D., Columbia Univ., and MANFRED M. MAYER, Ph.D., Johns Hopkins Univ., with a foreword by MICHAEL HERDELBERGER. Pp. 567; 86 ills. Springfield, Ill.: Charles C Thomas, 1948. Price, \$8.75.

INVESTIGATORS and technicians working in the fields of immunology, allergy, biochemistry, and medicolegal procedures will be well-served by this book on laboratory techniques. The emphasis here is on the methods of quantitative measurements dealing with antigens and antibodies primarily. Relatively few theoretical considerations are presented unless they apply directly to the methods of measurement. Kabat and Mayer have utilized an extensive literature in the field to illustrate the handling of experimentally obtained results with tables and graphs of data. The text is well-written by authors who have had an extensive experience investigating immunochemical processes. Techniques now in use for detecting Rh blood factors and antibodies have not been considered, but otherwise the scope of the book is broad and thorough. J. F.

**THE CHILD IN HEALTH AND DISEASE.** By CLIFFORD R. GRULEE, M.D., Rush. Prof. of Pediatrics, Univ. of Illinois, and R. CANNON ELEY, M.D., Harvard Univ. Pp. 1066; illustrated. Balt.: Williams & Wilkins, 1948. Price, \$12.00.

This new textbook of pediatrics should immediately take a proper place in the forefront as one of the leading texts in the specialty. As is the trend nowadays with "complete" presentations, a large group of collaborating experts rather than a single author or pair of authors have been responsible for the subject matter. The almost innumerable subjects which come within the scope of pediatrics have been covered, including adolescence, surgical conditions, and growth and development; yet the allotments of space have been kept in proper proportion to the practical importance of the respective topics. The book can be recommended as an authoritative and up to date text, of special interest to students, practitioners, and also as a desk reference. I. W.

**THE 1947 YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY.** Edited by HOWARD T. KANSNER, Prof. of Pathology, Western Reserve Univ., HERBERT Z. LUND, and ARTHUR HAWLEY SANFORD, Profs. of Clinical Pathology, Univ. of Minnesota. Pp. 558; 102 ills. Chicago: Year Book Publishers, 1948. Price, \$3.75.

THE Year Book of Pathology was a war casualty, this being the first volume since 1941, with abstracts limited to articles published in 1947. In addition they have added valuable material by inviting leaders in a few active fields of research to submit concise reviews.

The book is divided into 2 major parts, general and special pathology 312 pages, and clinical pathology 224 pages. The articles to be abstracted were well chosen but not infrequently the abstracts fail to give a clear idea of the contents of the original article. Even so the main purpose of the book is accomplished if it calls the readers' attention to articles they may wish to read in the original. For this purpose it can be recommended. W. S.

#### NEW BOOKS

*Hydrops congenitus universalis beim Kaninchen, eine erbliche fetale Erythroblastose.* By HANS NACHTSHEIM und HANS KLEIN. Abhandl. d. deut. Akad. d. Wiss. zu Berlin. Pp. 71; 25 ills. Berlin: Akademie-Verlag, 1948. Price, 7.50 DM.

*Cornell Conferences on Therapy.* Vol. 3. Edited by HARRY GOLD, M.D., et al. Pp. 337. New York: The Macmillan Company, 1948. Price, \$3.50

*Annual Review of Microbiology.* Vol. II. Edited by CHARLES E. CLIFTON, SIDNEY RAFFEL, Stanford Univ., and H. ALBERT BARKER, Univ. of California. Pp. 532. Stanford, Cal.: Annual Reviews, Inc., 1948. Price, \$6.00.

This, the second of a useful series, contains articles on 18 subjects ranging from general topics such as bacterial metabolism to the more specific spirochetes, yeasts, and so on.

*Dementia Praecox.* By LEOPOLD BELLAK, M.D., Assoc. in Psychiatry, New York Medical College. Pp. 456. New York: Grune & Stratton, 1948. Price, \$10.00.

This is an important book on an important subject. It is a comprehensive summary of the work done in the field from 1936-1946 (initial study by Dr. Nolan Lewis along the same lines was published in 1936). W.P.

*Medical Clinics of North America, Philadelphia Number, November 1948, Recent Advances in Gynecology and Obstetrics.* Pp. 1483-1771. Phila.: W. B. Saunders, 1948. Price, \$15.00 a year.

This volume gives the present-day views concerning a wide variety of frequently met problems, such as menstruation and menstrual disorders, management of the menopause, leukorrhea, ovarian cysts, the Rh factor, cancer detection and problems of pregnancy. In addition, it contains a useful 3-year index. This issue maintains the high standards of the series. H.H.

*The Frontal Lobes.* Edited by JOHN F. FULTON, M.D., CHARLES D. ARING, M.D., and S. BERNARD WORTIS, M.D. Proc. of the Assoc. for Research in Nervous and Mental Disease. Vol. 28. Pp. 901; 237 ills. Balt.: Williams & Wilkins, 1948. Price, \$12.50.

The 37 chapters of the 4 parts (Biology of the Frontal Lobes, Experimental Studies, Chemical Studies, Frontal Lobotomy) of this comprehensive report are aimed at "a critical evaluation of both the physiological basis of the lobotomy procedure and the clinical results which have so far been obtained."

*Emergencies in Medical Practice* Edited by A. ALLAN BURCH, M.D., F.R.C.P., Chas. Farm Hospital, England. Pp. 468; 113 ills., 8 in color. Balt.: Williams & Wilkins, 1948. Price, \$7.00.

*Psychiatry for the Millions.* By BENZION LIBER, M.D., Prof. of Psychiatry. Pp. 307. New York: Frederick Fell, 1949. Price, \$2.95.

*Personality Projection in the Drawing of the Human Figure.* By KAREN MACIVER, Ph.D. Pp. 181. Illustrated. Springfield, Ill.: Charles C Thomas, 1949. Price, \$3.50.

An outline of a method of personality analysis based on the interpretation of the subject's drawings of the human figure. The principles of such an analysis are surveyed in a tentative way, though "reasonably verified" through thousands of drawings correlated with their individual case records. To the casual reader interpretations often seem fantastically far fetched, though no more so than those applied to much of modern art.

*An Introduction to Physics in Nursing.* By HESSEL HOWARD FLITTER, R.N., M.A. Pp. 179; 99 figs. St. Louis: C. V. Mosby, 1948. Price, \$3.25.

*Adolescence Problems.* By WILLIAM S. SADER, M.D., F.A.P.A., Consulting Psychiatrist, Columbus Hospital, Chicago. Pp. 466. St. Louis: C. V. Mosby, 1948. Price, \$4.75. The experiences of a specialist in the field for more than 40 years offered as a help to physicians, parents and teachers.

*Psychological Medicine.* Modern Trend series. Edited by NOEL G. HARRIS, Civil Consultant in Psychological Medicine to the Royal Navy. Pp. 450. New York: P. B. Hoeber, 1948. Price, \$10.00.

Of the 19 chapters, 17 are by British authors. Consideration of the differences from American procedure—numerous but seldom important—should be interesting and valuable to specialists in the field.

*Recent Progress in Hormone Research.* Proceedings of the Laurentian Hormone Conference. Edited by GREGORY PENCUS. Pp. 378. Illustrated. New York: Academic Press, 1949. Price, \$7.80. This Volume III contains 12 articles on 5 aspects of hormone research.

*Anesthesia: Principles and Practice, a Presentation for the Nursing Profession.* By ALICE M. HUNT. Pp. 148. New York: G. P. Putnam's Sons, 1949. Price, \$2.60.

*Hearing is Believing* By MARIE HAYS HEINER. Introduction by RUPERT HUGHES. Pp. 126. Cleveland and New York: World Pub. Co., 1949. Price, \$2.00.

A book written to help the hard of hearing and the deaf by one of them.

*Proceedings of the New York Pathological Society.* Edited by ANTONIO ROTTINO. Pp. 80. 1948. Price not given.

*Medical Statistics from Graunt to Farr.* By MAJOR GREENWOOD, D.Sc., Prof. Emeritus of Epidemiology and Vital Statistics, Univ. of London. Pp. 73. New York: The Macmillan Company, 1948. Price, \$2.00. The 1941 and 1943 Fitzpatrick Lectures on the History of Medicine.

*Elementary Anesthesia.* By WILLIAM N. KEMP, M.D., Children's Hospital, Vancouver, Canada. Pp. 289; 100 ills. Balt.: Williams & Wilkins, 1948. Price, \$5.00.

There may well be a need for a textbook designed for the "busy undergraduate,—and the busier practitioner", but such a book should be accurate and authoritative. This volume is neither. It is full of outdated theories, incorrect statements and poor advice. A few examples: on page 12 is copied an old diagram which confuses the earotid sinus with the earotid body; on the next page a statement "the respiratory center is probably situated in the pons and upper medulla," based on a 1923 reference and ignoring the recent work of Pitts;

a grossly inaccurate discussion of the dangers of excessive absorption of carbon dioxide by closed system methods of anesthesia. Coramine is recommended as the "one analeptic which far surpasses all others in effectiveness," a statement that would find but little support. The book cannot be recommended. R. D.

*Studies in Analytical Psychology.* By GERHARD ADLER, Ph.D., Fellow of the British Psychological Society. Pp. 250; 19 ills. New York: W. W. Norton, 1948. Price, \$4.00.

THIS book is chiefly an exposition of the psychological concepts of C. G. Jung. It contains 6 papers which describe such things as the differences between Jung's analytical psychology and Freud's psychoanalysis, methods of procedure, the conception of the collective unconscious and archetypes, the ego and the life-cycle, the point of view of analytic psychology to religion, and Jung's contribution to modern consciousness. The book will be of interest to people who are thoroughly familiar with the field of psychiatry as an exposition of certain controversial ideas, theories and techniques. Even if the school of thought which is presented does not meet with universal agreement, the book is worth reading. W. P.

*The Management of Binocular Imbalance.* By EMANUEL KRIMSKY, M.D., Adjunct Prof. of Ophthalmology, New York Polyclinic Medical School. Pp. 464; 200 ills. Phila.: Lea & Febiger, 1948. Price, \$12.50.

THE author deals with such problems as: "1.) The meaning of binocular cooperation in all visual or accommodative ranges as well as for selective directions of gaze. 2.) The examination of binocular status in an objective or purposeful manner 3.) When to interpret binocular coordination as normal or flexible . . . 4.) How binocular imbalance can affect visual function . . . 5.) The significance of symptomless . . . binocular imbalance. 6.) How to treat . . . when the eyes appear straight. 7.) When cross-eye is apparent, how shall we evaluate it from the standpoint of the need of possible . . . therapy? 8.) When shall we prescribe prisms? 9.) When shall we resort to medical or surgical treatment? 10.) What are the merits of binocular training?" (Author's preface.)

*Psychiatry in General Practice.* By MELVIN W. THORNER, M.D., D.Sc., Asst. Prof. of Neurology, Graduate School of Med., Univ. of Penna. Pp. 659. Phila.: W. B. Saunders, 1948. Price, \$8.00.

THE author, believing that "most preventive psychiatry lies in the hands of the general practitioner", has written this book as "an attempt to lift psychiatry out of the realm of terra incognita for those whose primary efforts are spent in other fields." The book has good points, but suffers in comparison with "Teaching Psychotherapeutic medicine" (the excellent report of a joint effort sponsored by the Commonwealth Fund to teach practical psychiatry to general practitioners). Many case presentations are included which are often written in a short-story type of style. There appears to be more practical information in the section on methods than in other sections of the book. Some important subjects are inadequately discussed: for example, the importance of the doctor-patient relationship in therapy. The question of suicide, though mentioned in several case histories, is not considered adequately. (For comparison see Maurice Lévy "Psychotherapy in Medical Practice", Macmillan, 1942.) W. P.

*The Commonsense Psychiatry of Dr. Adolf Meyer.* Edited, with Biographic Narrative, by ALFRED LIEF. Pp. 677. New York: McGraw-Hill, 1948. Price, \$6.50.

MR LIEF, author of several biographies, has skillfully assembled and edited 52 reports, journal articles, and addresses of Dr. Adolf Meyer, the eminent psychiatrist. Biographical chapters are interspersed between some of the sections which contain Dr. Meyer's writings. The book is in no sense a text book of psychiatry. It is, rather, a presentation of the life, thoughts, speeches, writings, and philosophy of America's most outstanding psychiatrist. In view of the tremendous influence which he has had on psychiatry, and in view of the relative inaccessibility of most of his writings, this book is a valuable contribution. The whole medical profession, but especially that portion of it which is in the field of Psychiatry, owes a real debt of gratitude to Mr Lief. W. P.

*Pediatric Anesthesia.* By M. DICBY LEIGH, M.D., and M. KATHLEEN BELTON, M.D., Vancouver General Hospital, Canada. Pp. 240, 84 ills. New York. The Macmillan Company, 1948. Price, \$5.50.

THIS is the first monograph to appear on this important subject. The foremost achievement of the authors is to indicate the wide variety of methods of anesthesia that can be used in children. To a reader familiar with pediatric anesthesia, the book may be a disappointment, as a relatively insignificant portion of the text concerns itself with discussions of the great number of perplexing problems of child anesthesia. Technique is emphasized almost to the exclusion of theory. However, considered as a book on technique, it will be a valuable addition to the library of the anesthetist who occasionally does pediatric anesthesia. J. E.

*Synopsis of Psychosomatic Diagnosis and Treatment.* By FLANDERS DUNBAR, M.D., et. al. Pp. 501; 12 ills. St. Louis: C. V. Mosby, 1948. Price, \$6.50.

THIS book will be of interest and practical use to general practitioners and students of medicine as well as to the specialist in the "functional" (emotional) aspects of disease. It is well organized and contains in summary form a reflection of the most important studies and findings in the field. It also includes a useful list of references. W. P.

#### NEW EDITIONS

*Diseases of the Ear, Nose, and Throat.* By DOUGLAS G. CARRUTHERS, M.B., Ch.M. (Sydney), F.R.A.C.S. 2d ed. Pp. 344; 140 ills. Balt.: Williams & Wilkins, 1948. Price, \$7.00.

*A Synopsis of Physiology.* By A. RENDLE SNOW, Late Prof. of Surgery, Univ. of Bristol, C. L. G. PHARR, Fellow of Christ's College, Cambridge, and C. C. N. VASS, Reader in Physiology, Univ. of London. 4th ed. Pp. 346, 23 figs. Balt.: Williams & Wilkins, 1948. Price, \$6.00.

*Healthful Living.* By HAROLD S. DIEHL, M.A., M.D., Sc.D., Prof. of Preventive Medicine and Public Health, and Dean of the Med-

ical Sciences, Univ. of Minnesota. 3d ed. Pp. 595; 46 figs. New York: Whittlesey House Health Series. McGraw-Hill, 1949. Price, \$4.50.

"In this book he offers a simple guide on the subject of health for all who are interested in getting the most out of the body with which they began life, in avoiding the snares for the unwary, and in developing for the future a race of men and women capable of carrying on the tradition of healthfulness." (Dr. Fishbein's foreword.)

*Introduction to Organic and Biological Chemistry.* By L. EARLE ARNOW, Ph.D., M.D., and HENRY C. REITZ, Ph.D. 2d ed. Pp. 795,

90 ills. St. Louis: C. V. Mosby, 1949. Price, \$5.75.

With the advances achieved in this field in the 6 years that have passed since the 1st edition, it is not surprising that a radical revision has had to be performed—whole new sections added, and changes and expansions of many others.

*Common Skin Diseases.* By A. C. ROXBURGH. 8th ed. Pp. 497; 212 ills., 8 in color. Phila.: Blakiston, 1948. Price, \$7.00.

This text continues the good features of the earlier editions with much added new material, well documented usually by British references. The chapter on varicose veins, eczema and ulcer has been rewritten. A text with 8 editions in 16 years speaks for itself.  
H. B.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### OBSERVATIONS ON PENICILLIN-TREATED CARDIOVASCULAR SYPHILIS\*

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THERE have been only a few reports in the literature on the effect of penicillin in a significantly large number of patients with late cardiovascular syphilis. An important reason for this is the fact that many clinicians have been reluctant to use so potent a spirocheticidal agent in patients with syphilitic heart disease because of the fear of inducing a serious Herxheimer reaction and also because of the possibility of too rapid healing resulting in the so-called therapeutic paradox. This is a carry-over from the pre-penicillin days when it was the rule in most clinics to prepare all patients with cardiovascular syphilis with a preliminary course of bismuth or mercury before administering the more potent arsenicals.

Rather early in the penicillin era Dolkart and Schwemlein<sup>3</sup> described 2 patients with aortic regurgitation who

experienced untoward reactions while under penicillin therapy. One of the patients developed severe attacks of angina and ventricular extrasystoles soon after treatment was started. The second experienced intermittent substernal pain after 700,000 units of penicillin. Callaway and his group<sup>2</sup> reported as a possible illustration of therapeutic paradox, a patient who suffered the rupture of an aortic cusp several weeks after completion of penicillin therapy.

Moore, in his recent monograph,<sup>7</sup> reported on 12 cases of active cardiovascular syphilis which had been treated with penicillin at the Johns Hopkins Hospital. These patients had aortic regurgitation, aneurysm, or syphilitic aortitis with coronary ostial stenosis and angina of effort. Six of the patients also had neurosyphilis. In each case

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With collaboration of John H. Stokes, M.D., Edwin N. Hesbacher, M.D., George D. Gammon, M.D., Herman Beerman, M.D., Norman R. Ingraham, Jr., M.D., and John W. Lentz, M.D., and the technical assistance of Verna Mayer Stein, Emily Stannard, Jane Barbara Taylor, R.N., and Mildred F. Wills, R.N.

penicillin was started in very small dosage and then gradually increased over a period of days in an effort to avoid a Herxheimer reaction. There was one possible instance of therapeutic shock in this series of cases. This was in a patient who died on the fourth day of combined fever (malaria) and penicillin therapy. The autopsy revealed multiple plaques of syphilitic aortitis with fresh hemorrhages. The period of post-treatment observation in Moore's cases was too short to report on the therapeutic effect. One of the patients with a large aneurysm of the thoracic aorta died of rupture of the aneurysm 6 months after completion of treatment.

There is some doubt now that reducing the initial penicillin dosages actually prevents the occurrence of Herxheimer reactions since they have been observed following small doses. Olan-sky<sup>8</sup> recently reported on 6 patients (4 infectious syphilis and 2 late syphilis) in each of whom initial injections of 1,000 Oxford units of penicillin produced a febrile Herxheimer reaction. Incidentally, in this report Olan-sky reiterates the belief that penicillin even in small doses should not be administered to patients with late or complicated syphilis until a course of bismuth has been given. Stokes and Steiger<sup>11</sup> found that a reduction of the initial dosage to 500 units in early infectious syphilis was not sufficient to prevent Herxheimer reactions.

Russek and his co-workers<sup>10</sup> treated 15 patients with syphilitic aortitis, including 4 cases of aortic aneurysm, with relatively large doses of penicillin—40,000 units every 2 hours for 85 doses. Their paper deals principally with the incidence of reactions; the follow-up period of 1 to 3 months was too short to evaluate the efficacy of the treatment. Only 1 patient suffered an untoward reaction which might have been attributed to penicillin—relatively mild substernal pain which disappeared

despite continuance of penicillin. In 4 patients it was felt that there was definite improvement in coronary reserve manifested by decrease of substernal pain on exertion. Electrocardiographic improvement did not occur. These workers conclude, on the basis of these observations, that the risk of untoward reactions from penicillin in cardiovascular syphilis is small. They also maintain that the small risk entailed may be justified by the therapeutic results obtained.

Tucker and Farmer<sup>12</sup> have recently reviewed 34 cases of cardiovascular syphilis which were treated with penicillin: 25 had aortic insufficiency and 9 had saccular (thoracic) aortic aneurysms. These patients were started on treatment with dosages ranging from 500 to 100,000 Oxford units every 3 hours. The total dosages varied from 2 million to 15 million Oxford units. Five of the patients experienced febrile reactions early in the course of treatment (one of these after an initial dose of only 500 units), and 2 patients who had been having anginal attacks continued to have them during and following the administration of penicillin. In no case was it felt necessary to interrupt the penicillin therapy. The authors postulate that the febrile reactions which occurred in their cases may have been related to the concomitant neurosyphilis which each of these patients had. They conclude: "The absence of reported severe reactions proved to be due to treatment with penicillin tends to confirm our impressions that the dangers of severe untoward reactions may have been unduly emphasized."

**Method of Study.** This report is based on a study of 50 patients with cardiovascular syphilis who were admitted to the Institute for the Study of Venereal Disease between 1943 and 1948 (Table I.)

In the beginning cardiac studies included a physical examination, orthodiagram, and a pre-penicillin electrocardiogram. Later, when it was found that in patients with early infectious syphilis there were electrocardio-

graphic abnormalities which showed changes during penicillin therapy, it was decided to have the records repeated at approximately 3 day intervals during the course of treatment to determine if changes also occur in late cardiovascular syphilis. Six patients in congestive failure were under digitalis during the course of penicillin therapy; this was considered in interpreting their electrocardiograms.

Forty of the 50 patients had received metal chemotherapy previously. However, most of them had received no antisypilitic treatment for several years and only 4 patients in the entire group had had any treatment within a period of 3 months prior to the administration of penicillin.

some 15 of the patients were started with doses of 40,000 to 80,000 Oxford units every 2 hours.

**Results. AORTITIS.** There were 23 patients with uncomplicated syphilitic aortitis. We are cognizant of the fact that the clinical diagnosis of uncomplicated syphilitic aortitis is often a very difficult one, especially in the presence of hypertension and, or, arteriosclerosis. However, only those patients in whom the evidence for aortitis (especially fluoroscopic) was marked were included in the study.

TABLE 1.—DATA PERTAINING TO 50 PATIENTS WITH CARDIOVASCULAR SYPHILIS

	No. Cases	Age	Sex M F		Race W N		Ht. enlarge or hypert.	Cardiac symptoms	Ttl. No.	No. of patients on whom ECG were made				Therapeutic shock (Herxheimer)	Treatment stopped because of symptoms
										Before Abnormal ECG	During ECG Ttl. No.	Changes	After* Ttl. No.		
Aortitis	23	26 to 69	15	8	13	10	9	2	23	6(a)	11	3	16	4(b)	0
Aortic insuff.	20	38 to 66	19	1	12	8	18	8(c)	20	11	13	2	13	3(d)	0
Aneurysm	5	47 to 67	4	1	2	3	3	2	5	1(e)	2	1	4	1(f)	0
Aneurysm & aortic insuff.	2	43 to 69	2	0	1	1	0	2(g)	2	1	2	2	1	1(h)	0

(a) Probable ancient posterior infarction in one.

(b) All febrile.

(c) Marked congestive failure in five.

(d) All febrile.

(e) History of posterior infarction in one.

(f) Precordial constriction on third day of treatment.

(g) Congestive failure in one.

(h) Had recurrent attack of cardiac asthma on third day.

\* ECG changes not listed as they are still being followed up.

All of the patients were given sodium penicillin in aqueous solution on a round-the-clock schedule. In the early days the crude amorphous substance was used and, when it became available, crystalline penicillin-G. The total penicillin dosages ranged from 1,200,000 to 9,600,000 Oxford units. At first, all patients with cardiovascular syphilis were started on small doses (500 to 5,000 units every three hours for the first 24 to 48 hours) and gradually increased over a period of several days until a dose of 40,000 to 80,000 Oxford units every 2 or 3 hours was reached. Later, when it was found that reducing the initial dosage did not necessarily prevent the occurrence of a Herxheimer reaction<sup>8,11</sup>

These patients ranged in age from 26 years to 69 years. The sex and race distribution were as follows: 10 white males, 3 white females, 5 Negro males, and 5 Negro females. Eighteen of the patients also had central nervous system syphilis, 1 had a gumma of the lip, and 1 had diabetes mellitus. At the time penicillin treatment was instituted 21 of the 23 patients had positive blood serologic tests for syphilis.

The initial penicillin doses ranged from 500 to 80,000 units and the total



dosages from 1,200,000 to 9,600,000 Oxford units.

Only 2 of the 23 patients had experienced cardiac symptoms prior to penicillin therapy; they had complained of paroxysmal dyspnea. Eight were found to have slight cardiac enlargement and 1 moderate enlargement.

tients completed the prescribed course without further untoward reactions.

Six of the group with simple aortitis had electrocardiographic changes before penicillin. Five showed abnormal T waves in the limb and chest leads. In 1 patient the T waves in Lead I and II, CR<sub>1</sub> and CR<sub>5</sub> were inverted; in 2

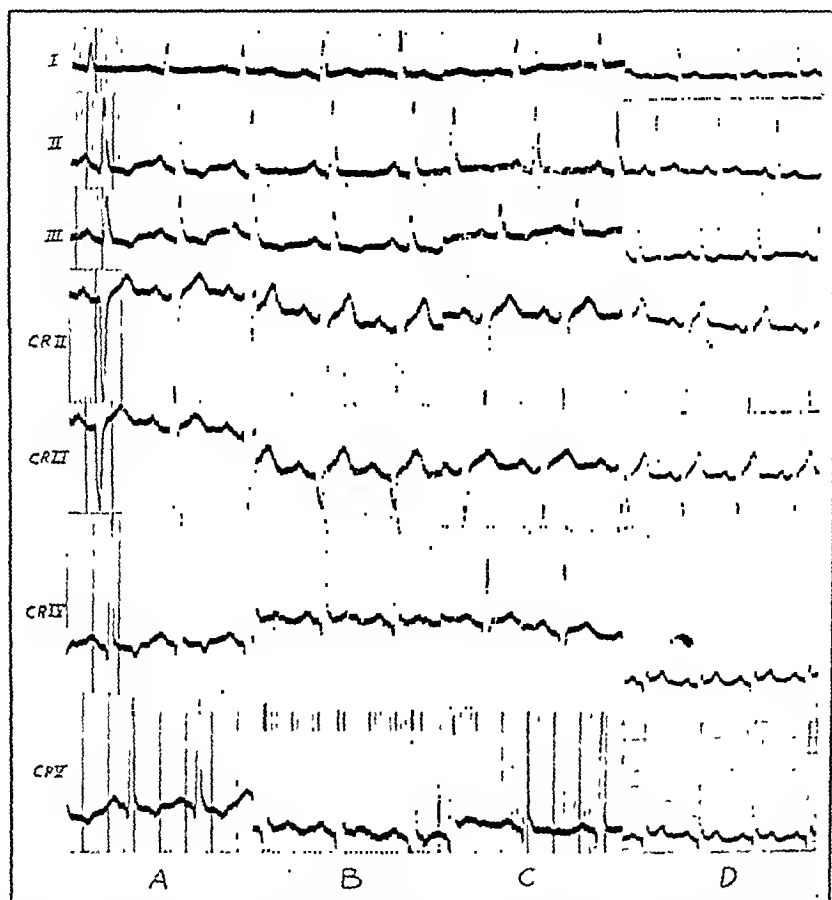


FIGURE 1.—COLORED MAN, AGE 38, WITH DEFINITE EVIDENCE OF AORTITIS.

A. Record made 4-23-47, before penicillin.

B. 4-26-47 after approximately 1.5 million units of penicillin.

C. 4-29-47 after 4.2 million units of penicillin. An electrocardiogram on 5-2-47 was similar to C.

D. 1-3-48 Eight months after penicillin. An ECG on 4-3-48 was similar to D.

Four patients experienced transient temperature rises within 24 hours after penicillin therapy was started. These were interpreted as evidence of Herxheimer reactions. However, in no case was treatment interrupted and all pa-

tients the T waves were flat in Lead I, inverted in II and III and abnormal in CR<sub>1</sub> and CR<sub>5</sub>; in the fourth the T waves were inverted in II and III, diphasic in CR<sub>2,3,4</sub> and flat in CR<sub>5</sub>; in the remaining case there were flat T waves

in Leads I and CR<sub>5</sub>. The sixth abnormal electrocardiogram had deep Q waves in Leads II and III, which suggested a healed posterior infarction. In 3 of the 5 cases showing pre-penicillin T wave changes, electrocardiograms were made during treatment; 2 showed temporary improvement in T waves, but later retrogressed to the pre-penicillin state. The other patient had marked T wave changes before treatment, improved considerably during treatment and continued to show improvement 1 year later (Fig. 1). One patient in whom pre-penicillin electrocardiograms were abnormal (T wave changes) had a normal tracing 4 months after completion of treatment. Unfortunately, electrocardiograms were not made during treatment.

One patient developed angina pectoris, with concomitant electrocardiographic changes ten months after penicillin.

**AORTIC INSUFFICIENCY.** There were 20 patients with aortic insufficiency ranging in age from 39 to 66 years. The sex and race distribution were as follows: 11 white males, 8 Negro males, 1 white female. Eighteen also had central nervous system syphilis. All had positive blood serologic tests for syphilis.

Although it has been known that aortitis and its complications are more common in males, the ratio of 19 males to 1 female in our series is unusually high. This is not the result of selection, but actually represents all the individuals with aortic regurgitation who came under our observation.

The initial and total penicillin dosages were the same as those used in uncomplicated aortitis.

Only 3 patients in this group experienced temperature elevations (all within the first 16 hours) after treatment was started, and all completed the prescribed course of therapy.

Eight of the patients had experienced

cardiac symptoms prior to penicillin therapy. Three had dyspnea on exertion, and angina pectoris; 1 had an old coronary occlusion. Five of the patients were in congestive failure and required bed rest, digitalis, ammonium chloride, and mercurial diuretics. It is of interest that each of these individuals was given penicillin concomitantly with the measures to correct cardiac decompensation and all of them left the hospital in an improved condition. Although this is admittedly too small a group upon which to base definite conclusions, it suggests that penicillin treatment of cardiovascular syphilis need not be delayed because of cardiac decompensation.

Eighteen of the 20 patients had enlarged hearts. In the 2 whose cardiac silhouettes were within normal limits of size the configuration suggested left ventricular hypertrophy.

In the group of 20 cases of aortic regurgitation, 10 showed significant T wave inversions and 2 had bundle branch block before treatment. Incidentally, 1 of the patients with inverted T waves also had auricular fibrillation; the only important arrhythmia noted in the entire group of 50 cases. In 4 instances T<sub>1</sub> and the T waves of CR<sub>1</sub> were inverted or diphasic; in 4, T<sub>2</sub> was also diphasic or inverted and in 2 the T waves of all limb leads were inverted. Of the cases with bundle branch block, 1 had right bundle branch block (with wide S waves), the T waves in Leads II and III were inverted and the T waves in Leads CR<sub>3</sub>, CR<sub>4</sub>, and CR<sub>5</sub> were diphasic. The other showed left bundle branch block of the discordant type. One of the patients with T wave changes showed slight electrocardiographic improvement during treatment; subsequently however, the T wave changes became more marked. Another patient who had slight electrocardiographic changes before treatment developed inverted T waves in Leads I, II, and

III, and abnormal T waves in CR<sub>4</sub> and CR<sub>5</sub> during his course of penicillin. A follow-up electrocardiogram made 3 months after treatment showed considerable improvement although the tracing was not normal. Still another patient (Fig. 2) showed abnormal T

waves before treatment and marked improvement 5 months later; this was also associated with definite improvement in his general condition.  
AORTIC ANEURYSM. There were 5 patients with aortic aneurysm ranging in age from 47 to 69 years. The distribu-

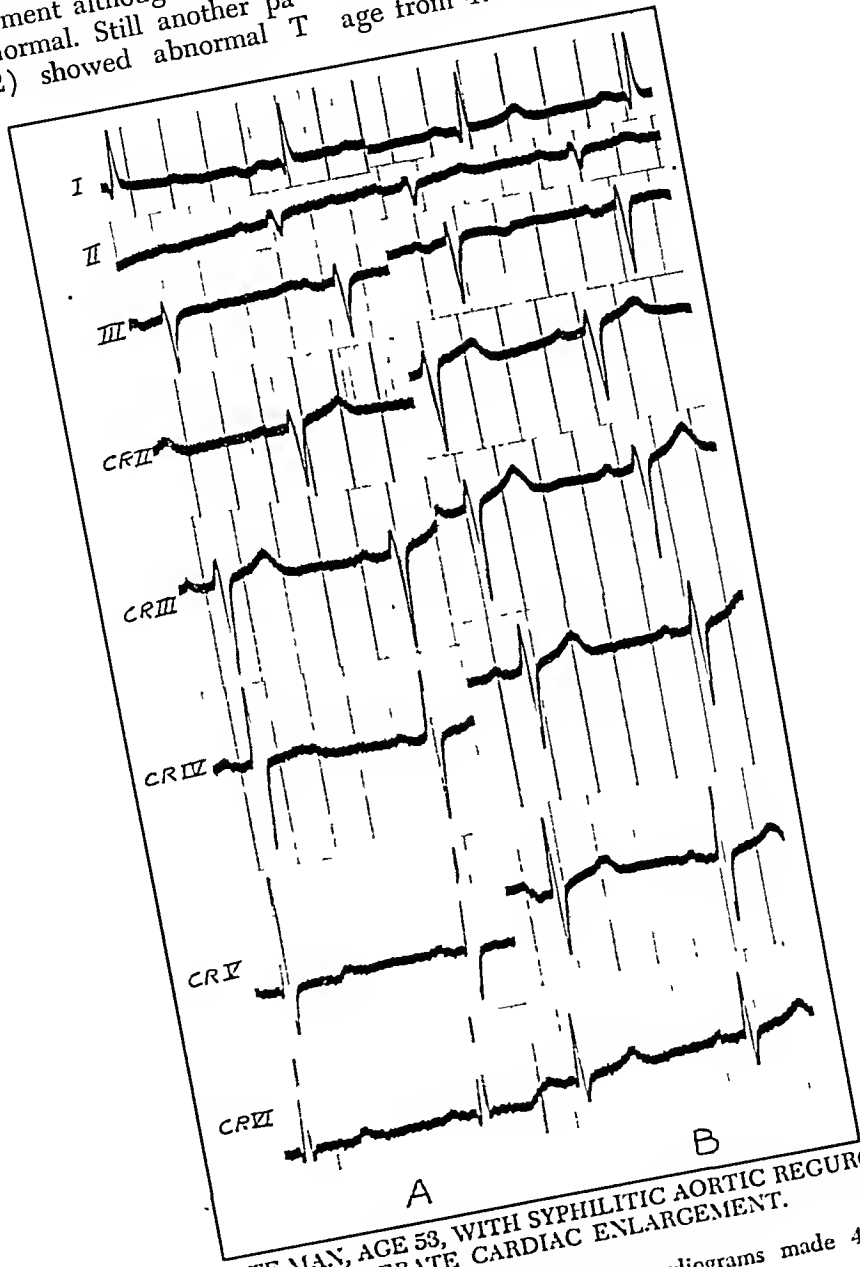


FIGURE 2.—WHITE MAN, AGE 53, WITH SYPHILITIC AORTIC REGURGITATION AND MODERATE CARDIAC ENLARGEMENT.  
A. Record made 12-8-45, before penicillin.  
B. 5-11-46 after 2,400,000 units penicillin. Electrocardiograms made 4-4-47 and 6-1-48 were similar to B.

tion by sex and race was as follows: 2 white males, 2 Negro males, and 1 Negro female. One patient in the group had central nervous system syphilis. All had positive blood serologic tests for syphilis.

The initial penicillin dosages ranged from 500 to 80,000 Oxford units and the total dosages from 3,600,000 to 9,600,000 units.

None of the patients experienced a febrile reaction during treatment. A 54 year old Negro female complained of slight precordial constriction for several hours on the third day of treatment. According to her history she had experienced no cardiac symptoms prior to the administration of penicillin. She completed the course of treatment without interruption of the schedule.

Three of the 5 patients with aneurysms had enlarged hearts. One patient in the group, who also had hypertension, showed an abnormal electrocardiogram in which there were inverted T waves in Leads II and III and flat T waves in CR<sub>5</sub>. These changes became more marked during treatment and have remained so on follow-up, but they were probably in part due to digitalis.

**AORTIC ANEURYSM AND AORTIC RECIRCULATION.** There were 2 patients with both aortic aneurysm and aortic insufficiency. One was a 43 year old white male, the other a 69 year old Negro male. The former also had central nervous system syphilis with a Type III spinal fluid. Both had positive blood tests.

The older man was admitted to the hospital in marked cardiac failure. There was no definite history of previous antisyphilitic treatment. His failure had been progressive over a period of about 4 years. Penicillin was started in small doses (500 units) on a 2 hour schedule. He had no untoward reactions until the third day of treatment, when maximum dosage was reached

(40,000 units every 2 hours). He then experienced an attack of severe substernal oppression and dyspnea similar to those he had on frequent occasions before treatment. Penicillin dosage was reduced from 40,000 to 10,000 Oxford units every 2 hours for the next 48 hours and then increased again to 40,000 units every 2 hours; the patient completed a course of 4,800,000 Oxford units without further untoward reactions. His pre-treatment electrocardiogram revealed flat T waves in the limb leads and slight inversion in CR<sub>3,4,5</sub>. There was slight improvement in the electrocardiograms made on the third and thirteenth days of treatment. On follow-up 4 months after treatment he felt much improved and had experienced only 2 slight attacks of dyspnea. Examination disclosed no signs of congestive failure.

The other patient had experienced dyspnea on exertion and precordial pain before treatment. He denied having received previous antisyphilitic therapy. Examination revealed aortic systolic and diastolic murmurs, dilatation of the ascending aorta evident on percussion and confirmed by orthodiagram. He was given a total of 2.4 million units of penicillin starting with 5,000 units every 3 hours and reaching a maximum dosage of 40,000 units every 3 hours after 36 hours. The pre-penicillin electrocardiogram was normal. There were no untoward reactions to treatment. He was re-treated 6 months later and this time received 2.4 million units of penicillin starting with the maximum dose of 40,000 units every 3 hours. An electrocardiogram made the day treatment was begun, showed slight T wave changes. On the second day the electrocardiogram showed inversion of T<sub>2</sub> and T<sub>3</sub> and slurring of the QRS complexes; by the fifth day the inversion was only slight; and on the last day the electrocardiogram was normal. Electrocardiograms

4½ and 6½ months later were also normal.

Comment. In no instance did we find it necessary completely to interrupt treatment because of untoward reactions. One patient who had an aneurysm and aortic regurgitation suffered an attack of cardiac asthma during treatment, but he had experienced similar attacks before penicillin. Another patient with aortic aneurysm developed slight precordial constriction on the third day of treatment, but the symptoms were not entirely typical of angina pectoris.

The lack of untoward symptoms in patients with severe myocardial lesions is most noteworthy. Two patients with probable ancient posterior infarctions experienced no untoward reaction to penicillin therapy. Five patients with aortic regurgitation and one with aortic regurgitation and aneurysm who were in marked cardiac failure were treated with penicillin at the same time measures were taken to combat congestive failure; not only did they tolerate both treatments very well, but all were markedly improved on discharge. This is contrary to the accepted belief that patients with cardiovascular syphilis in cardiac failure do not tolerate potent spirocheticidal drugs.

In the pre-penicillin era both cardiologists and syphilologists were of the opinion that antisyphilitic treatment should be postponed in cases of congestive failure until compensation was restored. Although this is too small a group on which to base definite conclusions, our observations suggest that congestive failure in syphilitic heart disease may not be a contraindication to immediate penicillin therapy.

No clear-cut case of therapeutic paradox was observed in this series of patients. As stated previously, the fear of this phenomenon has influenced clinicians to treat cardiovascular syphilis very cautiously. In the era of metal

chemotherapy full doses of arsenicals were often never given. One might raise the question whether this did not result in too little treatment. It is most difficult to evaluate symptoms in a condition where the pathologic changes are such that untoward symptoms are prone to occur with or without treatment. Arteriosclerosis is not infrequent in individuals with syphilitic aortitis. It is conceivable that coronary occlusion occurring during the course of antisyphilitic treatment is not due to the so-called therapeutic paradox, but sclerotic coronary vessel or ostium. to the coincident closure of an arterio-Sudden death in syphilitic aortitis and spontaneous rupture of an aneurysm cannot be considered unusual with or without treatment. Therefore, the appearance of severe symptoms during treatment does not *per se* indict the treatment as the cause.

It is well known that T wave changes may be due to numerous factors other than heart disease, but to the best of our knowledge, with the exception of digitalis in the decompensated cases, such factors were not operative during this study. The effects of digitalis were considered in the interpretation of the electrocardiograms. T wave and RS-T segment changes may occur in a small percentage of normal young individuals. In 3107 such cases<sup>4,5,14</sup> only 15 (0.5%) showed T wave changes in Lead II, and in none was the T wave in Lead I inverted. In Wood, Wolferth and Miller's<sup>14</sup> studies of an older age group inverted T waves in Leads I and II were associated with cardiovascular disease in all cases followed. In our group of 50 patients only 7 (14%) were under the age of forty.

Although a fairly large percentage (30%) of our cases showed electrocardiographic abnormalities either before, during, or after treatment with penicillin, one cannot conclude that they were all directly or solely due to

the syphilitic infection. Arteriosclerosis undoubtedly was present in many patients in the upper age groups, and in others, especially those with aortic regurgitation, the ECG abnormalities were in part at least of the type seen in left ventricular hypertrophy. Conversely, the changes in the T waves which occurred as the result of treatment with penicillin cannot be construed as being due to alterations in the arteriosclerotic state or the left ventricular hypertrophy due to damaged aortic valves. Webster and Reader<sup>13</sup> demonstrated at autopsy, active inflammation in the aortas of inadequately treated patients with syphilitic aortitis. Hu, Lin, Chen, and Frazier<sup>14</sup> reported the isolation of virulent *Treponema pallidum* from the aortas of patients, dying from cardiovascular syphilis, 32 hours after death. In view of these findings, one may speculate that changes within actively involved tissue about the orifices of the coronary vessels may be responsible for electrocardiographic abnormalities during and following treatment with such a potent spirocheticidal agent as penicillin. Because of the great differences of opinion among pathologists<sup>1</sup> as to the interpretation of myocardial scars and small cellular foci found at postmortem examination of patients with cardiovascular syphilis, it is impossible to form an opinion as to whether any of the abnormalities are due to syphilitic involvement of the myocardium. The possibility that there may be changes in chemical constituents of the blood during penicillin therapy which may cause T wave changes must also be considered, although we are not aware of any studies on this subject.

There are clear indications that penicillin is of value in the treatment of syphilitic heart disease, especially in patients where the pathologic process is not far advanced. However, it would be unwise to draw too sweeping or

definite conclusions concerning individual items of beneficial effect at this writing. Prolonged observation of a larger group of cases is needed. The fact that the course of syphilitic heart disease is variable and often unpredictable was borne out in a recent report by Reader and his associates.<sup>9</sup>

We are continuing to re-examine the patients at intervals and intend to report their status at some future date.

**Summary.** 1. Fifty patients with cardiovascular syphilis were treated with sodium penicillin in aqueous solution in total dosages ranging from 1.2 to 9.6 million Oxford units. Only 4 patients in the series had received metal chemotherapy within a 3 month period prior to penicillin. There were 23 diagnosed uncomplicated aortitis, 20 with aortic insufficiency, 5 with aortic aneurysms, and 2 with both aneurysms and aortic insufficiency.

2. There appeared to be no relationship between the amount of penicillin in the initial dose and the occurrence of a febrile Herxheimer reaction.

3. More than half of the patients<sup>25</sup> had electrocardiograms at approximately 3 day intervals during the course of treatment. Electrocardiographic changes (significant T wave changes) were noted during the course of treatment in 8 patients.

4. In no instance was it deemed necessary to discontinue penicillin because of untoward reactions.

5. The 6 patients who were in congestive failure were able to tolerate penicillin simultaneously with the measures for counteracting cardiac decompensation. Thus, contrary to the heretofore accepted practice of giving no potent spirocheticidal drug to decompensated cardiovascular syphilis patients, it does not seem necessary to delay penicillin treatment until compensation is restored.

6. There has been no unequivocal instance of "therapeutic paradox" in

this series during the period of observation, though sufficient time has not yet elapsed to warrant drawing definite conclusions.

7. The material thus far studied indicates that penicillin is a valuable agent in the treatment of syphilitic heart disease.

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# THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

## A Report of 24 Cases Treated with Penicillin

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THE therapy of subacute bacterial endocarditis has always presented a challenge to the physician, and it is only since the introduction of penicillin that anything approaching encouraging mortality statistics has been achieved. In Table 1 the relative effectiveness of the various therapeutic methods that preceded the antibiotics is compared with penicillin.

TABLE 1.—RESULTS OF DRUG THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

Method	Recoveries
Spontaneous	1-3 %
Sulfonamides	0-3.4% <sup>6,11</sup>
Sulfonamides plus Fever	12.1% <sup>3</sup>
Sulfonamides plus Heparin	23.3% <sup>3</sup>
Massive I. V. Sulfadiazine	37.5% <sup>11</sup>
Penicillin	70-80 %

Although the sulfonamides appreciably raised the incidence of cures, their use entailed a high treatment fatality risk. Schein and Baehr,<sup>11</sup> in their report of sulfadiazine therapy, listed a 6% mortality due to treatment. The use of heparin, thought to be warranted by some investigators as an adjunct to the sulfonamides by allowing increased penetration of the fibrin clot, is in itself not without danger from hemorrhagic complications.

Twenty-four cases of subacute bacterial endocarditis (including 2 of subacute bacterial endarteritis) have been treated with penicillin at the Henry Ford Hospital since 1944. Due to the scarcity of the drug during the early period, several of these cannot be thought to have been treated adequately by present standards. A review of the literature on penicillin treatment

in various clinics reveals considerable variation in daily dosage, method of administration, and duration of therapy. Only after a larger number of penicillin-treated cases have been reported and analyzed, can criteria for effective management be established.

*Age, Sex, and Cardiac Lesion.* Twelve of our cases were males and 11 were females. The distribution throughout the various age groupings is found in Table 2. Three cases under 20 years of age had congenital cardiac lesions, 2 having patent ductus arteriosus with superimposed infection and the third a patent interventricular septum. The remaining 20 cases were of rheumatic etiology; 13 involving the mitral valve alone, 2 the aortic valve alone, and 5 combined involvement of both mitral and aortic valves.

TABLE 2.—AGE DISTRIBUTION

Age Grouping	No. of Cases
10-19	4
20-29	3
30-39	6
40-49	7
50-59	2
Over 60	1

At autopsy one case (No. 20, Table 8) was found to have a bicuspid aortic valve, but this was taken to be due to erosion and secondary separation of the valve attachments from the commissures rather than a congenital defect. Three of our cases manifested auricular fibrillation at the time of diagnosis (incidence of 12.5%).

Table 3 shows the length of time that symptoms had been present before



a definite diagnosis of subacute bacterial endocarditis was made. Because of its insidious onset and protean character, the disease frequently remains unrecognized for long periods and is often misdiagnosed during the early stages. The frequency of presenting symptoms corresponded, in the main, with a previous series reported from this hospital and with those from other clinics.<sup>6,12</sup>

TABLE 3—DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS

Time	No. of Cases
Less than 3 weeks	3
3 weeks to 3 months	9
4 months to 6 months	6
7 months to 1 year	6

*Organisms and Sensitivity.* (See Table 4). In 2 of our cases, both aerobic and anerobic blood cultures were repeatedly negative. In both instances the history, clinical findings, and sub-

organism was not inhibited by 50 units per cc. of penicillin but was inhibited by 20 units per cc. of streptomycin.

*Dosage, Duration of Therapy, and Mode of Administration.* The total dosage of penicillin varied from 1,800,000 units to 194,000,000 units (average, 26,900,000 units). The average daily dose was 800,000 units. Duration of therapy varied from 16 to 97 days (average, 34.5 days). The wide variation in dosage and length of treatment was influenced partly by the response to therapy in each case and partly by the scarcity of penicillin during the early part of the series.

Various routes of administration, with the exception of the oral, were used (see Table 5), and in many instances 2 or more routes were tried in the same patient. In many cases the

TABLE 4—BACTERIA FOUND AND THEIR SENSITIVITY TO PENICILLIN

Organism	Cases	Sensitivity to Penicillin Units/cc.	Cases
Neg culture	2		2
Strep viridans	18	.005	7
		.05	4
		.25	1
		Not inhibited by 50	1
		Not done	5
Non-hemolytic strep.	2	.005	2
Staph aureus	1	.05	1
Hemolytic Staph. albus	1	Not done	1

sequent course confirmed the diagnosis beyond a reasonable doubt. Unfortunately, arterial punctures were not done, possibly they would have yielded the desired information.

Sensitivity to penicillin *in vitro* was determined in all but 6 cases. Of the more highly sensitive group (.005 units per cc. to .05 units per cc.) involving 15 cases, there was only one death, showing that there tends to be a practical relationship between organism sensitivity and therapeutic results. In one case (No. 20, see Table 8) the

continuous intravenous method was employed initially, to be replaced later by the intermittent intramuscular route due to the development of thrombophlebitis at the site of injection, despite the use of small amounts of heparin in the vehicle.

*Results.* Of the 23 patients, 5 are dead; the 18 alive are free from evidence of infection with subsequent periods of observation varying from 5 months to 4 years.

A patient was regarded as having relapsed when he was found to show

TABLE 5.—MODE OF ADMINISTRATION

Route	No. of Cases
Continuous Intravenous	8
Intermittent Intramuscular	4
Contin. Intrav. + Intermittent Intramusc.	10
Contin. Intravenous + Contin. Intramusc.	1
Intermit. Intramusc. + Penic. in Wax	1

TABLE 6.—DURATION OF CLINICAL OBSERVATION FOLLOWING CESSATION OF THERAPY

Length of Observation	No. of Cases
Less than 6 months	1
6 to 12 months	7
1 to 2 years	5
2 to 3 years	;
3 to 4 years	3

evidence of recurrent infection including a positive blood culture at any time within 1 year from the date of the cessation of treatment.<sup>3</sup> This occurred in 6 of our cases (as shown in Table 7) with eventual death in 4. One patient (Cases 16 and 17, see Table 8) had a re-infection 14 months following his first episode. On both occasions the organism was streptococcus viridans, but unfortunately no tests for penicillin sensitivity were made. Each time the clinical response to the drug was satisfactory. In the interval between infections the patient had an episode of fever and joint distress with negative blood cultures that responded promptly to the administration of salicylates and was considered to be acute rheumatic fever.

*Deaths.* Death occurred in 5 of our patients, 4 of whom had suffered one or more clinical relapses as shown above (Table 7). In 3 cases death was directly attributable to cardiac failure (Cases 6, 8, 20, see Table 8) and in one to infection plus cardiac failure (Case 5). In the remaining fatality (Case 7) death followed a subarachnoid hemorrhage.

*Other Therapeutic Measures.* Sulfonamides were employed in varying dosage in 8 cases. From a review of the case records the indications for the addition of this medication were not always obvious. In some of these cases the drug was not administered in adequate therapeutic dosage and its effectiveness was always difficult to evaluate.

In the 2 cases of bacterial endarteritis a patent ductus arteriosus was successfully ligated during the course of penicillin therapy.

Because of the extreme resistance of the organism (*Strep. viridans*) to penicillin in Case 20 (Table 8), streptomycin was administered in a dosage of

TABLE 7.—RELAPSES

Case No.	No. Relapses	Months Duration of Disease	Organism	Total Dosage Units in millions	Route†	End Result
7	5	12	strep. viridans	194.	CIV-IM	Dead. Subarachnoid Hemorrhage
6	2	1½	strep. viridans	1.8	CIV-IM	Dead. Cardiac failure
20	1	7	strep. viridans	9.*	CIV-IM	Dead. Cardiac failure
8	1	17	strep. viridans	36.	CIV	Dead. Cardiac failure
21	1	8	non-hem. strep.	9.	CIV	Well. 36 months
23	1	3	strep. viridans	16.	IM	Well. 13 months

† CIV—Continuous intravenous.

IM—Intramuscular.

\* Also received 96 gm. streptomycin.

TABLE 9.--DATA ON 24 CASES OF SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN

DRAKE, DENHAM: SUBACUTE BACTERIAL ENDOCARDITIS

Case #	Sex	Age	Heart lesion	Duration of symptoms	Organism	Sensitivity (units/cc)	Daily dosage (units in thousands)	Duration of therapy (days)	Total Penicillin (units in millions)	Duration of observation (months)	Sulfas	Recurrences	Deaths
1	M	40	AS MI Aur. lth.	5 mos.	Strep. viridans	0.005	CIV 200	21	4.2	47			
2	M	17	Patent ductus	5 mos.	Hemolytic Staph. albus	-	CIV - IM 100	18	1.8 Surg ligation	46	78 gm		
3	M	35	MI	3 wks.	Strep. viridans	0.05	CIV 200	21	4.2	11			Infection Failure
4	M	16	MI	1 wk.	Strep. viridans	0.005	CIV - IM 200	18	3.6		60 gm		Cardiac Failure
5	M	35	MI	5 mos.	Strep. viridans	0.005	CIV - IM 200	9	1.8		88 gm		Subacute Menorr.
6	M	49	MI AS MI	4 wks.	Strep. viridans	0.25	CIV - IM 80 2000	7 90	194.0				Cardiac Failure
7	M	44	MI AS MI	4 mos.	Strep. viridans	-	CIV 200 200 400	21 6 24	36.0	5		22 gm	
8	M	20	MI AS MI AS MI	1 yr.	Strep. viridans	-	600 1000 CIV - IM 500	12 30	15.0				
9	F	49	MI	10 mos.	Strep. viridans	0.005	CIV - IM 200 1000	16	14.4				
10	F	41	MI	6 mos.	Strep. viridans	0.05	CIV - IM 400	38	11.6 add amts. at home	7			
11	M	22	MI AS MI	7 mos.	Strep. viridans	0.005	CIV - IM 200	33	6.6				
12	F	14	MI AS MI AS MI	6 wks.	Strep. viridans	0.005	CIV 200 200 400	19	6.0				
13	M	48	MI AS MI	7 wks.	Strep. viridans	0.05							

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14	10	M	Patent IV Septum	12 mos.	Culture neg.	-	IM 400 800	50	38.4	7	
15	38	F	IM MS MI	5 mos.	Staph. Aureus	0.05	IM 800 2400	38	68.8	7	
16	36	M	IM MS MI Aur. Fib.	10 wks.	Strep. viridans	-	CIV 200 400	22	7.6	14	
17	Sure as patient 16			6 wks.	Strep. viridans	-	IM 800 1000 2000	40	48.0	11	
18	55	F	IM MS	7 mos.	Strep. viridans	0.005	CIV - IM 800 1000	36	31.2	15	
19	33	F	IM MS	10 days	neg. culture	-	IM 300 in oil 400 1000 2000	52	71.5	8	25 gm
20	34	M	IM AI Iheuspid aortic v.	10 wks	Strep. viridans	not inhib. 50.	CIV 600 8800 1000	13	9.8	3 1/2	89 gm 1 Cardiac Failure
21	65	M	IM MI	7 mos.	Non-hemolytic Strep.	20.0 Streptom.	1 gm 2 gm	48	96 gms.		
22	45	M	IM MS MI Aur. Fib.	10 days	Strep. viridans	0.005	CIV 200 400	36	9.0	38	• 1
23	58	M	IM MS MI	6 wks.	Strep. viridans	-	CIV - CIM 400 400	29	11.6	27	
24	23	F	Patent Ductus	6 wks.	Non-hemolytic Strep.	0.005	IM 200 400 800 200 320 400	18	16.6	16	19 gm 1
							CIV 400 500 1000	22	13.8	5	

\* Received prior to admission.  
 f CIV - Continuous intravenous.  
 IM - Intramuscular.  
 CIM - Continuous intramuscular.

2 gm. daily for 48 days. Vestibular manifestations consisting of dizziness and nystagmus began soon after starting treatment and persisted until death from congestive heart failure. Clinical arrest of the infection was apparently accomplished, although 1 positive blood culture was obtained 2 months prior to death.

**Discussion.** Although it is important to establish a standard plan for the treatment of subacute bacterial endocarditis, it is necessary that the physician be ready to regulate the therapy to suit the requirements of the individual patient. Factors to be taken into consideration include the duration of the disease at the time the diagnosis is made, clinical condition of the patient, nature of the offending organism and its response to penicillin *in vitro*, record of any previous therapy, and the symptomatic and clinical response of the patient after treatment is under way.

The supportive measures are those necessary in any long continued infectious process. Diet should be high in calories and easily tolerated. A low sodium intake is indicated in view of the significant incidence of congestive failure. Transfusions are usually unnecessary but should be used without hesitation if one is faced with a dangerously low or falling hemoglobin value during therapy. Digitalis is indicated only if congestive failure develops. Oral iron preparations are useful to combat the secondary anemia, and high potency multivitamin mixtures may be desirable in general supportive care. Strict confinement to bed is not necessary or advisable in the absence of symptoms or signs suggestive of the onset of congestive heart failure.

Penicillin is the specific therapeutic agent of choice in the majority of cases. The various better known fractions (F, G, K and X) have not as yet been

evaluated sufficiently to know which is most effective.<sup>2</sup> Streptomycin should be employed in those cases involving gram negative organisms or where penicillin resistance has been demonstrated by *in vitro* laboratory tests. Anticoagulants as an adjunct to aid in the penetration of the valvular vegetations by the antibiotics seem superfluous and not without danger, although Loewe still advocates the use of heparin.<sup>7</sup> Sulfonamides have proved to be far inferior to penicillin (Table 1) and at present are to be considered only after adequate penicillin and, or, streptomycin therapy have failed.

A survey of the current literature reveals no unity of opinion regarding the daily dosage of penicillin, the duration of therapy, and the optimum route of administration.

Various clinics have recommended daily doses of penicillin varying from 200,000 to 1,200,000 units in the average case, and it would appear that, with this passage of time, the figures are being revised upward<sup>1,5,7,9,10,13</sup>. Theoretically, the sensitivity of the offending organism to penicillin should give us at least the starting point for estimating an adequate dose. If the causative organism is inhibited by 0.05 units or less of penicillin per cc. of culture media, one may expect therapeutic success with moderate daily doses. Tumulty and Harvey,<sup>13</sup> however, emphasize that many organisms appearing resistant will respond to an average dose. It is also true that some organisms which appear sensitive to *in vitro* tests will not respond to the corresponding dose of the drug. In general, it seems advisable to administer the drug in doses which will give a blood level 5 to 10 times the minimal amount effective *in vitro*. In the treatment of relapses a substantial increase in both the daily dose and the duration of treatment should be made regardless of the *in vitro* sensitivity of the organism.

The clinical response of the patient to a given dosage schedule will regulate the subsequent schedule. Within the first few days the patient should show clinical signs of improvement. The persistence of occasional embolic episodes early in the course of treatment need not be construed as an indication of therapeutic failure.

Loewe<sup>7,8</sup> and also Christie<sup>1</sup> have utilized both intravenous and intramuscular routes of administration with success. Flippin and his associates<sup>2</sup> preferred the intermittent intramuscular technique with "booster" injections periodically in resistant cases. More recent reports<sup>10,13</sup> suggest use of the intermittent intramuscular route for average doses and utilization of the continuous intravenous method only if the daily dose is to be 3,000,000 units or greater. The final choice of route should be determined by the ease of administration and comfort of the patient in the cases calling for moderate doses of the drug. If the continuous intravenous route is used, 5% glucose in water as a vehicle rather than normal saline should be employed due to the undesirable amount of sodium introduced by the former method. The frequent occurrence of thrombophlebitis at the site of administration and the inconvenience to the patient incurred by this method leads us to favor the intermittent intramuscular route. We have occasionally employed the "booster" doses as advocated by Flippin and have found them to be advantageous.

Loewe<sup>8</sup> estimates that with the continuous intravenous method a blood level of approximately 1 unit per cc. may be obtained for each 1,000,000 units of the drug given daily. This determination may be used as an initial guide in estimating the dosage based on *in vitro* sensitivity of the organism. Although significant elevations of the blood level of penicillin have been reported by the concurrent use of various

compounds such as para-amino-hippuric acid and caronamide, our experience along this line has been limited. Certainly the use of these compounds seems to offer promise in selected cases.

Tumulty and Harvey<sup>13</sup> point out that the goal of any therapeutic regimen is the cure of the maximum number of patients and not the determination of the smallest amount of a therapeutic agent which will be effective in the majority of patients. For this reason, it does not seem extravagant to over-treat some patients in order to secure adequate treatment of all. The authors mentioned above cite 4 cases with apparent clinical arrest of the infection who died from other causes and at autopsy still showed evidence of active endocarditis. Christie<sup>1</sup> emphasizes the duration of the treatment, irrespective of the total dosage, as an important factor.

At the present time there is no general agreement as to the criteria for adequate treatment. Priest *et al.*<sup>9</sup> state: "The only consistently reliable guides after cultures of the blood have become sterile are the leukocyte count and the blood sedimentation rate." Tumulty and Harvey,<sup>13</sup> on the other hand, believed that the best indications of effective therapy were the return of the temperature and pulse to normal, a gain in weight, the absence of sweats, an increasing sense of well being of the patient, the subsidence of embolic phenomena, and the elevation of the red count and hemoglobin toward normal. We believe that the clinical response of the patient is a more reliable index to adequate therapy than laboratory determinations. Duration of therapy based upon the above standards will vary in individual cases, but 5 weeks should probably be regarded as a minimum for continuous therapy in uncomplicated cases.

Relapses usually occur within 3 or 4 weeks after cessation of therapy and,

in our experience, are usually of serious prognostic import (see Table 7). Therapy should be resumed, a more intensive program used, and streptomycin administered where indicated as previously outlined. The largest total dosage in our series was 194,000,000 units, although a case has been reported which was given a total of 1,450,000,000 units with recovery.<sup>13</sup>

Considerable difference of opinion exists as to whether cardiac failure is hastened due to further scarring of the valves during the healing process. It must be conceded, however, that successful therapy for subacute bacterial endocarditis by increasing longevity of this group of patients will magnify the importance of congestive failure as a cause of death in rheumatic heart disease.

As pointed out above, the occurrence of embolic episodes during the course of treatment is not necessarily evidence of inadequate therapy, although its frequent occurrence probably indicates the need for prolongation of the course of the drug.

The occurrence of thrombophlebitis at the site of continuous intravenous injections has already been discussed, and we have not encountered necrosis of muscle secondary to intermittent intramuscular administration.

The use of penicillin prior to and following dental extractions and tonsillectomy in patients with valvular heart disease is definitely warranted. Recent work suggests that an effective penicillin level should be continued for at least 48 hours post operatively.<sup>4</sup> Foci of infection should be diligently searched for in all patients undergoing therapy for subacute bacterial endocarditis and, if possible, should be eliminated during the course of penicillin treatment.

The final determinants of success in the therapy of this disease with penicillin are not primarily such factors as age, duration of the disease, or the valves involved, but rather the degree of cardiac disability, the critical nature of the embolic phenomena and the resistance of the offending organism.<sup>13</sup>

Our mortality rate of 21.7% compares favorably with 374 cases collected from the recent literature whose overall death rate was 26.6%.<sup>1,5,7,9,10,13</sup> It is to be expected that refinements in antibiotic therapy in the future will significantly improve upon this figure by eliminating failures due to recurrent infection.

**Summary.** A total of 24 cases of subacute bacterial endocarditis treated with penicillin involving 23 patients is reported in detail. Eighteen are living and free from evidence of infection 5 months to 4 years following cessation of treatment.

A correlation between sensitivity of the organism *in vitro* and the *in vivo* response to antibiotic therapy is demonstrated. The importance of clinical relapse as an unfavorable prognostic sign is pointed out.

Factors to be considered in setting up a rational program of therapy are discussed. The importance of congestive heart failure as a complication is stressed and suggestions for its prevention are outlined.

Streptomycin is advocated for those cases in which a marked *in vitro* resistance or a lack of clinical response to massive doses of penicillin is encountered.

An overall mortality of 21.7% for this series compares favorably with other series previously reported.

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# MODIFICATION OF THE CARDIAC OUTPUT AFTER INTRAVENOUS INJECTION OF HYPERTONIC GLUCOSE SOLUTION

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GLUCOSE is known as one of the most important nutritive substances for muscular tissue, and its stimulating action on the heart in the heart-lung preparation has been shown by Bayliss, Muller and Starling<sup>1</sup>. Glucose therefore, has been recommended in the treatment of patients with cardiac disease and is usually used intravenously in hypertonic solutions at a concentration from 20% to 50%<sup>9,10</sup>. However, quantitative determinations of the effect of glucose on the work of the human heart, to our knowledge, have not yet been reported. The present study has been performed in order to measure the modification of the cardiac output induced by hypertonic glucose solution. The determinations of cardiac output have been made by the ballistocardiographic method of Starr<sup>12</sup>. The effect of the injection has been studied in normal subjects and in patients with cardiovascular disease.

**Technique.** The subjects were studied at least 2 hours after a meal and a control ballistocardiographic record was taken after 15 minutes rest. Then they received an injection of 50 cc. of a warm glucose solution at a concentration of 50%; the injection was always made intravenously in 20 to 40 seconds. A series of ballistocardiographic records were taken successively at 1, 2, 3, 4, 5, 6, 8, 10, 15, 20 and in a few cases up to 45 and 60 minutes. The results are calculated in percentage of minute output modification of the control record. Only increases of 10% or

more above the control record were regarded as significant.<sup>14</sup>

Blood pressure was estimated at intervals by the sphygmomanometer in some, but not all of our subjects. No significant changes were found after the injection and, as we preferred not to disturb the subjects in any way, we omitted these estimations in the last part of the study.

These determinations have been made in 9 subjects with normal hearts, and in 14 patients with evidence of heart disease (2 with questionable heart disease, 2 with arteriosclerotic heart disease, 3 with congestive failure of variable etiology, 6 with hypertension and 1 with nephrosis). All of the patients with cardiac disease were ambulatory at the time of the test and all were capable of reclining on the ballistocardiographic table without severe orthopnea.

The results were subjected to a statistical analysis by the methods of Fisher<sup>5</sup> and the word "significant" is used in the statistical sense, indicating a probability of less than 5 in 100 that the difference was due to chance.

**Results.** The data are given in Table I. In normal subjects, the hypertonic glucose solution induced an augmentation of the cardiac output lasting about 5 minutes after the injection. The maximum augmentation reached 10% to 30%. After 5 to 8 minutes, the cardiac output reached its normal level, and in many cases dropped thereafter to a lower level.

A strikingly different response was obtained in the great majority of our patients with cardiovascular disease. The augmentation of the cardiac out-

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put lasted much longer than in normal cases and was generally still present 15 or 20 minutes after the injection. In some subjects, however, we observed a transient drop of the cardiac output during the first minutes following the injection and a later increase.

In making the statistical analysis it seemed best to exclude the patients with questionable cardiac disease (Patients 10 and 16) even though their inclusion would have made no material difference.

The average duration of the increased cardiac output in patients with cardiac disease is very significantly longer than in the normal group; indeed there is no overlapping of the two groups. The difference between the maximal increase of cardiac output, expressed as percent of the control value, is significant but less striking. The mean maximal increase is 35.9% in the cardiac group and 19.3% in the normal group. In 3 cardiac patients (Patients 18, 19 and 23) the maximal increase in cardiac output was 50% or more; these increases stand out from the other data. If these 3 results are excluded from the cardiac group, its mean increase becomes 25.2% instead of 35.9% and statistical analysis reveals that this value is not significantly different from the normal average.

The modifications in cardiac output were not correlated with any significant change in heart rate, indeed the rate changed but little in most experiments. However, in 1 normal subject (Patient 8 in the Table) a transient slowing of the heart beat occurred from the first until the second minute after injection.

**Discussion.** As successive estimations of cardiac output by the ballistocardiogram agree within 10% (the standard error of estimation of the second from the first is 4.8% of the second value<sup>14</sup>), our results show that hypertonic glucose solution induces an augmentation

of the cardiac output both in normal subjects and in those with cardiac disease. As the blood pressure did not change significantly in the subjects studied, the work of the heart must have increased. In normal subjects this augmentation was transient; in cardiac disease it was much more prolonged.

Glucose, therefore, is another example of the group of physiological agents which affects the cardiovascular systems in disease in a manner different from the effect produced in healthy persons. This is also true of such familiar agents as digitalis<sup>2,13,11</sup> and theophylline ethylene diamine<sup>6</sup> injected intravenously; and doubtless of many other agents. And it is of no little interest that all three of the agents mentioned above cause a stimulation of the circulation more pronounced and enduring in disease than in health.

The action of hypertonic glucose that we have demonstrated might have been brought about by the glucose itself, by the hypertonicity of the injected solution, or by both means. In normal subjects the augmentation of the circulation was transient. A similar effect has been observed after the injection of hypertonic saline solution<sup>7</sup> and this raised the question whether the response is due to their common property, hypertonicity, rather than to a specific effect on the heart. It is known that hypertonic solutions attract a certain amount of water from the tissues into the blood, increasing the blood volume and the venous pressure<sup>1</sup>. Whether this latter fact could explain the initial augmentation of the cardiac output, in accordance with Starling's Law of the Heart, was investigated and the results are recorded in the following paper.

On the other hand, the long lasting augmentation of the output observed in cardiac patients might be due to a beneficial action of glucose on the heart. It should be recalled that in

TABLE 1.--CHANGES IN CARDIAC OUTPUT AFTER INTRAVENOUS INJECTION OF 50 CC. OF 50% GLUCOSE

Case	Diagnosis	Remarks	Minutes After Injection											
			1	2	3	5	6	8	10	15	20	30	45	60
1. JH	Normal													
2. JN	Normal		+8	+8	+1	+1	-8	-4	-4	-9	-7			
3. JC	Normal		+15	+20	+20	+6	+1	-1	-1	-3	+1			
4. JB	Normal		+17	+15	+2	+1	0	-4	-8	-15	-10			
5. G	Normal		+26	+17	+2	+1	0	-4	-9	-7	-20			
6. IB	Normal		+12	+22	+29	+4	+10	0	-12	-12	-17			
7. IH	Normal		+1	+6	+6	+1	+1	0	0	0	0			
8. JA	Normal		+6	+13	+2	+1	-5	0	0	-11	-11	-15	-15	
9. SS	Normal		+30	-10	0	+4	0	0	+7	+5	0	0		
10. CD	Normal?		+14	+23	+30	+4	+10	0	-5	-8	-7	-7		
11. IB	Articel. lit. dis.	With transient slowing of heart rate	+24	+10	+10	+17	+17	+15	0	-7	-5	-7		
12. JH	Articel. lit. dis.		+28											
13. VC	Comp. Failure													
14. AG	Comp. Failure													
15. BA	Comp. Failure													
16. BU	Normal?		+7	+15	+15	+14	+13	+13	+13	+13	+10	0	-11	
17. DS	Hypertension		+25											
18. LF	Hypertension		+63	+24	+24	+21	+21	+12	+29	+25	+25	+20		
19. BL	Hypertension		+91	+68	+45	+41	+26	+26	+17	0				
20. GU	Hypertension		-3	+4	+4	+14	+14	+14	+14	+14	+7	+5		
21. KC	Hypertension		+22	-1	-3	-3	+1	+2	+4	+5	+18			
22. LG	Hypertension		+29	0	+5	+9	+5	+5	+9	+11	+19	+19		
23. JF	Nephros- is		+50	+50	+43									

The numbers indicate the percentage of modification in cardiac output above or below its level before the injection

animal preparations, glucose has a more favorable effect on the contractility of a failing heart than of a powerful heart<sup>1,3</sup>. Our results indicate that the same may be true in human beings.

Of those patients with cardiac disease who showed a prolonged increase in cardiac output, there was no apparent common factor except cardiac abnormality. It was our impression that the most striking increases and prolongations of cardiac output were roughly proportional to the degree of dyspnea and perhaps to the degree of cardiac insufficiency, but this relationship is not too clear. Patient 16, aged 17, with meningo-vascular syphilis, had no evidence of cardiac disease except an abnormal electrocardiogram, yet his cardiac output remained elevated for 15 minutes after the glucose injection.

None of the patients with cardiac disease stated that they felt any subjective benefit following the injection, nor were any unfavorable effects noted. Objections have been raised to the therapeutic use of hypertonic glucose solution in patients with coronary insufficiency. It has been reported in these cases to cause a significant alteration of the electrocardiogram; moreover some patients are reported to have

complained of severe precordial pain<sup>8</sup>. In our experiments the injection was always performed rapidly, but the only complaint recorded was a warm sensation throughout the body lasting a few seconds. Moreover, the maximal augmentation of the cardiac output immediately after the injection was usually not very great, and the heart was not subjected to a sudden increase in its work. In our one patient with true angina of effort (Patient 11 in the Table) anginal pain was not produced.

**Summary and Conclusion.** Hypertonic glucose solutions injected intravenously induced an augmentation of the cardiac output as measured by the ballistocardiogram, which generally reached 10% to 30% above the control figure.

Although the average maximal increase was significantly greater in patients with cardiac disease than in healthy persons, the difference was not striking; and, if the data obtained in 3 patients are omitted, the difference is no longer significant.

On the other hand the difference in duration of the effect was very striking and highly significant. The increased cardiac output lasted much longer in patients with cardiac disease.

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# ON THE MECHANISM BY WHICH INTRAVENOUS INJECTIONS OF HYPERTONIC GLUCOSE SOLUTION CAUSE INCREASED CARDIAC OUTPUT

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IN THE preceding paper<sup>8</sup> it was demonstrated that 50 cc. of 50% glucose solution injected rapidly intravenously was followed by a noteworthy increase in cardiac output which tended to be of longer duration in subjects with heart disease than in healthier subjects. Further studies have been undertaken to answer several questions about the mechanism of this effect.

As was mentioned in the previous paper, two possibilities presented themselves:

1. Hypertonic glucose solution would be expected to draw fluid into the circulation and to increase blood volume, and this might in turn raise the venous pressure and so stimulate the heart according to Starling's Law. According to this concept the increased effectiveness of the glucose in cardiac disease might be attributed to the excess tissue fluid present in such cases as manifest or occult edema. This fluid might be more readily available than the tissue fluids of healthy subjects and so might lead to a more rapid and prolonged increase in blood volume and so to more pronounced cardiac effects.

2. From the results of animal experiments, it was also proper to expect that glucose would stimulate the heart directly. Indeed, the enhanced effect in cardiac disease might be taken to be analogous to the results already obtained in animal preparations<sup>1,2</sup> in which a damaged heart responded more vigorously to glucose than hearts in better condition. This hypothesis is not

an alternative to the first and there was no way of testing it directly, but the problem could be approached by excluding other possibilities and finding whether the data were consistent with this concept.

The results demonstrate that, although a significant rise of blood volume did follow the injection of glucose, the increase of venous pressure was so small that it was often negligible and it could not be correlated with the increase in cardiac output. As there is positive correlation between the cardiac output effect and the level of blood sugar after glucose is injected, the data suggest that glucose produces an effect on the circulation directly by cardiac stimulation rather than indirectly by increasing the blood volume.

**Subjects.** The 22 subjects were all ward patients at the University Hospital and each received a complete hospital study. Four gave abnormal ballistocardiograms and as cardiac output could not be calculated with confidence from such records these data were not used. The patients who had normal ballistocardiograms were divided into 2 groups.

Included in the group with normal hearts was B. M., age 58, with carcinoma of the lung who died 7 weeks after the test and had a normal heart at necropsy. The rest were: T. S., age 54, diagnosed anxiety neurosis; L. B., age 42, with a mild pyrexia of unknown origin; J. Z., age 55, with a mild depressed psychosis; N. V., age 56, who suffered from loss of weight not explained by the study; and H. W., age 26, diagnosed psychoneurosis and primary dysmenorrhea.

Included in the group with abnormal hearts were: O. B., age 40, with luetic aortic valvulitis; L. M., age 29, A. S., age 30, and P. E., age 39, all with rheumatic mitral stenosis; E. M., age 57, with coronary heart disease,

left bundle branch block and angina pectoris; C. W., age 53, who came to the hospital with intermittent substernal pain which later became constant, who showed severe electro-

cardiographic abnormalities suggesting pericarditis rather than infarction, and who developed azotemia and left the hospital moribund; A. K., age 59, W. H., age 47, C. B.,

TABLE 1.--RELATION OF CHANGE OF CARDIAC OUTPUT PER MINUTE TO CHANGE IN PLASMA VOLUME AFTER INJECTION OF HYPERTONIC GLUCOSE

Subject	Diagnosis	Change in Cardiac Output and Plasma Vol.	Time After Injection at which Samples were Taken and Estimates Made.			
			3 to 8 min.	12 to 18 min.	25 to 30 min.	45 to 50 min.
E.M.	Coronary Ht. Dis.	C.O. per min.% P.V. %	+ 7 +12	+ 8 + 6	- 5 + 4	0 0
T.S.	Coronary Ht. Dis.	C.O. P.V.	+ 3 +18	+ 2 -12	- 5 0	0
P.E.	R.H.D. Mitral Stenosis	C.O. P.V.	+ 4 +16	+20 +14	+10 +11	
A.S.	R.H.D. Mitral Stenosis	C.O. P.V.	+26 +23	+16 +24	+ 6 +24	- 8 +19
L.M.	R.H.D. Mitral Stenosis	C.O. P.V.	+17 + 4	- 2 - 4	- 1 - 1	+ 7 -11
C.W.	Dissic. Aneurism (?)	C.O. P.V.	- 3 + 5	+12 + 3	+ 2 - 3	0 0
W.H.	Ess. Hypertension	C.O. P.V.	+ 5 +11	+ 9 +12	+ 9 +15	+20 +16
L.G.	Ess. Hypertension	C.O. P.V.	+12 + 9	+ 9 + 5	+ 9 +13	+10 + 6
A.K.	Ess. Hypertension	C.O. P.V.	+ 4 + 5	-11	-15 + 2	-25
B.M.	Normal Heart	C.O. P.V.	+12	- 8 - 4	- 7 - 4	
L.B.	Normal Heart	C.O. P.V.	+28 +16	+21 +16	+ 4 +10	+ 3 +19
J.Z.	Normal Heart	C.O. P.V.	+ 3 +12	+ 3 + 7	- 6 - 1	- 4
N.V.	Normal Heart	C.O. P.V.	- 7 +11	- 7 + 9	- 4 +14	- 3 + 8
	Average Change in C.O. (%)		+ 9.6	+ 5.5	- .2	0
	Average Change in P.V. (%)		+11.8	+ 6.3	+ 6.5	+ 7.1

age 27, L. G., age 62, O. Y., age 56, and A. M., age 42, had hypertension at or exceeding 180/105 mm. Hg. Of these six, 5 were adjudged to have cardiac abnormality because they had either cardiac enlargement by fluoroscope or a major electrocardiographic abnormality or both. However, C. B., the youngest of them, had no cardiac enlargement and a normal electrocardiogram, but the shape of the heart suggested left ventricular hypertrophy.

All these patients were in good functional condition (Class I) except P. E. who was in mild congestive failure at the time of testing (Class IV); O. Y., admitted in failure, who had recently recovered from it when the tests were made (Class III); and C. W. extremely ill, but with the diagnosis in doubt.

Methods. Plasma volumes were estimated by the dye dilution method using T-1824 according to the technique of Gregerson.<sup>3,4,5</sup> A single sample taken between 10 and 15 minutes after the dye injection was employed to calculate the initial blood volume. Later in the same experiment other blood samples were taken to follow the changing blood volume. The amount of dye in the plasma was estimated from optical density read in a Beckman Spectrophotometer. The changes in blood volume were estimated from the deviation of our samples from the theoretical time-disappearance curve of the injected dye. This curve had been previously determined<sup>5</sup> and I confirmed the findings in 4 subjects.

Hematocrit specimens were centrifuged at

a speed of 2500 to 3000 r.p.m. for half an hour.

Venous pressures were taken by the method of Moritz and Tabora, by allowing a saline solution to run into an antecubital vein as far as it would. The needle was left in the vein during the experiment.

Arterial pressures were estimated in the usual manner by the auscultatory method.

Cardiac output was estimated from the ballistocardiograms.<sup>9</sup>

In some experiments blood samples were analysed for sugar and occasionally for chlorides. I am indebted to Dr. J. H. Austin who made these estimates for me.

All patients were tested either fasting or at least 2 hours after a meal kept low in fat content. They lay horizontally on the ballistocardiograph for 15 minutes before the first record was taken. Venipuncture was then performed. Dye was injected, venous and arterial pressures were measured and a ballistocardiogram taken. After these estimations, 50 cc. of 50% glucose was injected in a period of about 30 to 40 seconds. Ballistocardiograms, blood samples and estimations of venous and arterial pressure were taken at intervals for the next 45 minutes or until the effect had died away. Not all the estimations were made on every subject.

Results. *Plasma volume* was estimated repeatedly on 4 of the subjects with normal hearts and on 9 of the group

TABLE II.--RELATION OF CHANGE OF CARDIAC OUTPUT TO CHANGE OF VENOUS PRESSURE AFTER INJECTION OF HYPERTONIC GLUCOSE

Subject	Diagnosis	Change in Cardiac Output and Venous Pressure	Time After Injection at which Samples were Taken				
			2-3 min	5 min.	8-10 min	10-15 min	20-30 min
O Y.	Ess. Hypertension	C.O. Per min % V P mm H <sub>2</sub> O	+ 6 + 1	+17 - 4	+ 6 - 3	+13 + 1	+10 - 1
G B	Ess. Hypertension	C.O. V.P.	+ 4 +22	- 3 +11	- 1 + 2	- 1 - 6	- 2 -11
O B	Lactic Ac. Disease	C.O. V P.	+20 +12		+16 +16		+12 +12
E.M.	Coronary Ac. Disease	C.O. V P	+ 6 +12	- 8			- 5 + 8
L. G.	Hypertension	C.O. V P	+ 9 +13	+ 5	+15 - 1	+ 9 - 8	+10 - 1
N V.	Normal Heart	C.O. V P.	+ 8 +17	+20	+ 5 +20	- 7 - 3	- 4 + 4
H #	Normal Heart	C.O. V P.	+ 8 +32	- 1 +30	-11 +22	-11 +17	-15 +15
B M.	Normal Heart	C.O. V P		+12		- 8 +16	- 7 +12
	Average Change in C.O. (%)		+ 9	+ 5	+ 5	0	0
	Average Change in V P (mm H <sub>2</sub> O)		+21	+12	+ 6.5	+ 3	+ 3

with cardiac disease. The results are given in Table 1. Inspection of the results showed no noteworthy difference between those obtained in the two groups of cases. After the injection of glucose the plasma volume always increased, the average increase for all our subjects being +374 cc. at the end of 5 minutes, +221 cc. between 12 and 18 minutes, +225 cc. between 25 and 30 minutes and +242 cc. in the smaller group tested between 45 and 50 minutes.

Forty-five estimates of cardiac output can be paired with simultaneous estimates of plasma volume. Statistical analysis shows that the correlation between the changes in these 2 values after glucose is significant, the correlation coefficient being 0.41, whereas any value over 0.29 is significant.

Hematocrit values were estimated repeatedly in 21 cases, 5 of whom did not receive glucose. The changes were usually very small; the average packed cell volume diminished 1.6% in 14 samples taken from 2 to 5 minutes after the injection of glucose; 1.9% in 13 samples taken from 10 to 15 minutes; 1.9% in 16 samples taken between 20 and 30 minutes; and 2.1% in 8 samples taken between 35 and 45 minutes. But a tendency towards diminution was also found in those cases not given glucose. Thus 35 to 45 minutes after a dye injection, no glucose being given, the average of 5 samples showed the packed cell volume to have diminished by 0.6%, a value not significantly different from that found after glucose at a similar time. For this reason, as well as the well-known error inherent in calculating the total relation between cells and plasma from blood samples drawn from veins, the results have been reported as plasma volume, rather than as blood volume. The latter was calculated in each case and the data did not change our conclusions.

*Venous pressure* was estimated re-

peatedly in 9 subjects of whom 3 had normal hearts and 6 had cardiac disease. The initial pressures were all within normal limits. Results are recorded in Table 2. After glucose there was a slight but definite increase of venous pressure in most subjects. The average increase reached a maximum, 20 mm. H<sub>2</sub>O, shortly after the injection, at the time when cardiac output was often at its maximum. This increase of venous pressure was not sustained and in about 10 minutes the average was only 6 mm. above the initial level. From this point the average fell more slowly and was only slightly above the initial level 35 minutes later.

Estimations of the change of venous pressure after glucose can be paired with simultaneous estimations of the change in cardiac output in 30 instances. No relation could be demonstrated as the correlation coefficient, 0.165 was not significant.

*Arterial pressure* was estimated repeatedly in 6 cases. No important changes were found after the injection in any case tested. A similar result having been secured in the preceding study these estimations were not continued.

*Blood sugar* was estimated repeatedly in 3 cases. As was to be expected from the many results secured by those interested in the Intravenous Glucose Tolerance Test,<sup>6</sup> a marked increase was found after the injection and the blood sugar remained abnormally elevated during the whole experiment. Table 3 gives these results. The correlation coefficient between blood sugar level and the cardiac output is 0.57, and any value over 0.51 is significant. The blood chlorides did not change significantly.

*Discussion.* The additional experience gained permits a more exact statement of the relation of the response to glucose and the clinical state of the patients. In this study the patients with cardiac abnormalities used



were not as sick as those tested previously<sup>8</sup> and it is interesting that their cardiac outputs did not increase so much, nor was the increase so prolonged as in the group studied before<sup>8</sup>.

The patients with abnormal hearts had been classified according to the functional classification of the American Heart Association before the results of the study were known, and it is of interest to compare this clinical estimate of cardiac capacity with our findings, using the data of both this and the preceding paper<sup>8</sup>. In so doing it seemed proper to omit case L.B. who had a fever of unknown origin and whose cardiac response to the glucose was much more vigorous and prolonged than that of any other person with a normal heart. No other patient was febrile. C.W. was also omitted because the primary diagnosis was in doubt, he was very sick and his cardiac status was hard to assess.

As the difference between the glucose effect on the cardiac and non-cardiac groups was most conspicuous late in the test, and as the exact times at which ballistocardiograms were taken varied somewhat, we studied values for cardiac output estimated from ballistocardiograms taken between 15 and 30 minutes after the injection of glucose and, if there was more than one estimate in this period, the average was used. The results were striking. In 14 patients with hearts judged to be normal the average cardiac output per minute at this time was 7% below the level found before injection. On 14 patients judged to have cardiac disease but without undue dyspnea on exertion (Class I) the average was 2% above the initial value at this time; in the 3 judged to belong to Class II the average was +16%; in the 5 in Class III, +12%; in the 2 unable to take any exercise without discomfort (Class IV) it was +22%. The numbers in the Classes II, III, IV are too small to

warrant statistical analysis of the data from each group separately, so they were combined. The mean obtained in the group with normal hearts is significantly different from that of the Class I group,  $t$  being over 3. Similarly the mean of the Class I group is significantly different from that of the combined groups,  $t$  being again over 3. Evidently the duration of the response to glucose increases as the functional capacity of the patient diminishes.

The results also throw light on the mechanism by which glucose produces its effect on the circulation. It is true that there is a significant correlation between the increase of blood volume that occurs after glucose and the increase of cardiac output; a similar significant correlation, of about the same magnitude, was found between changes of cardiac output and blood volume in cases subjected to operation<sup>7</sup>, but it does not necessarily follow that the one causes the other; in this instance it is more likely that the glucose is the single cause of the two effects. We know of no means by which increased blood volume could stimulate cardiac output except by raising the filling pressure of the heart; and the increase of peripheral venous pressure after glucose was negligible in most cases. Therefore, the increased blood volume could hardly have produced the striking cardiac effects observed. It is true that the greatest average height of venous pressure and the maximum average stimulation of cardiac output in the same subjects coincided at about 4 minutes after the injection, but the change in peripheral venous pressure was always very small, averaging only 2 cm. at this time. Warren *et al.*<sup>10</sup> have presented evidence that changes in cardiac filling pressure of this amount are not sufficient to affect the cardiac output consistently. Also if one examines closely the data on simultaneous estimations

of venous pressure and cardiac output (Table 2), the lack of correlation is readily seen. Calculation shows no significant correlation within the 30 pairs in which simultaneous changes in venous pressure and cardiac output could be compared. One must conclude that the increase in cardiac output is not to be attributed to an improvement in cardiac filling caused by increased blood volume.

cardiac function found. The results obtained on patient L.B. (the only subject with fever), Table 3, are in complete accord with this concept for the increase in cardiac output is closely related to the increased level of blood sugar. However, in patient J.Z. an even higher increase in blood sugar was not accompanied by a significant change in cardiac output and in L.G. (with hypertension) the fall of the blood

TABLE III.—THREE EXPERIMENTS SHOWING VARIOUS CHANGES AFTER GLUCOSE INJECTION

Case	Time	Pulse Rate	Blood		Cardiac Output	Plasma	Volume	Diagnosis
			Sugar mg p. 100 cc.	Chlorides M Fq/L.		cc.	%	
1. L.B.	Before glucose	98	80					Pyrexia of unknown origin (T.100-102°) Normal C V system
	After glucose 3 min.	106			+28			
	6 - 8 min.	103	213		+28	+443	+16	
	15-18 min.	102	223		+15	+455	+16	
	30 min.	100	196		+4	+274	+10	
	45 min.	100	176		+3	+553	+19	
2. J.Z.	Before glucose	62	78	103				Involutional melan- colic. Normal C V system.
	After glucose 3-5 min.	62	254	102.1	+3	+106	+12	
	8 - 15 min.	61	199	102.5	+4	+230	+7	
	30 min.	60	188	102.8	-6	-27	-1	
	45-50 min.	60			-1			
3. L.G.	Before glucose	57	90	107.1				Hypertensive C.V. disease due to chronic pyelo- nephritis
	After glucose 3 - 5 min.	52	236	106.4	+9	+386	+9	
	8 min.	53			+15			
	15-16 min.	55	208	105.9	+9	+214	+5	
	30 min.	56	176	107.2	+9	+637	+13	
	45 min.	58	156	107.4	+10	+287	+6	

Therefore, the second alternative must be considered; glucose might increase the cardiac output by a direct stimulating effect on the myocardium. A large amount of data on the Intravenous Glucose Tolerance Test<sup>6</sup> indicated that after an injection such as was employed, blood glucose would be increased for the duration of the experiment. This was confirmed in 3 subjects and the correlation between the blood sugar level and the change in cardiac output per minute is significant. So glucose, present in excessive amounts, may well have caused the increase of

sugar curve is not accompanied by a corresponding fall of cardiac output. Obviously other factors than the level of blood sugar influence the intensity of the cardiac effect which follows intravenous glucose.

The results show that the functional condition of the patient's cardiovascular system is one such factor.

**Summary and Conclusions.** Blood volume, peripheral venous pressure, blood sugar and blood chlorides have been measured before, during and after the increase in cardiac output follow-

ing the intravenous injection of 50 cc. of hypertonic glucose solution into healthy persons and cardiac cases. The results have been subjected to statistical analysis.

Although the blood volume increased after injection, and this was significantly correlated with the increase in cardiac output, the rise in venous pressure was almost negligible and no significant relation between the changes of venous pressure and the increase of cardiac output could be demonstrated. Therefore, no evidence was obtained that increased filling of the heart is an important factor in the cardiac stimulation which follows glucose.

Blood sugar increased markedly after glucose injection and the change in its

level was significantly correlated with the increase in cardiac output. Blood chlorides remained constant. Therefore the increase in cardiac output is best explained as a direct action of glucose on the heart, analogous to that well known to occur in experiments on the hearts of animal preparations.

The intensity of the cardiac action of glucose varied inversely with the clinical estimate of cardiac capacity, the average effect being most prolonged in those patients whose functional capacity was lowest. This again appears to be analogous to results secured in acute animal experiments, in which the heart is more strongly stimulated by glucose when it is in poor condition.

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# AMEBIASIS: EXPERIENCE IN THE JOHNS HOPKINS HOSPITAL, 1936-1946

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IN 1903 Futcher<sup>19</sup> first reported the experience with amebiasis in the Johns Hopkins hospital, at which time that disease was shown to be responsible for 0.74% of the admissions to the medical service, with a mortality rate of 25.3%. Since that time great strides have been made in our understanding of the pathogenesis, complications and treatment of amebiasis. No attempt to review comprehensively the literature relevant to the disease will be made here, since Craig<sup>11</sup> has quite adequately done so to 1944. During and since World War II great emphasis has been placed on the possible sequelae of tropical exposure of masses of American troops and the fear of increased incidence of amebic disease in this country expressed.<sup>2,26,36,50</sup> Many more recent reports have dealt with military personnel in whom relatively acute amebiasis was present; it seems worth while, therefore, to review the experience of a large civilian hospital in dealing with this problem.

**Material.** In this review, all hospitalized adult patients in whom a diagnosis of amebiasis in any form was made during the period extending from 1936 to 1946 inclusive, were studied. A total number of 296 cases were catalogued, 0.15% of the total hospital admissions over the same period. Of these cases 25 were not available for analysis, 39 were inadequately studied, or the diagnosis not satisfactorily established, and 27 cases were diagnosed on services other than the medical service and were excluded. The remaining 205 cases, all proven amebiasis by (a) demonstration of *Endameba histolytica* in the stools, or (b) specific response to emetine in extra-intestinal forms of the disease, were

carefully analyzed. This number constitutes 0.51% of the total number of admissions to the medical service during the period of study.

*Endameba histolytica* is a protozoan the laboratory identification and characteristics of which are beyond the scope of this review. Suffice it to say, it is primarily an intestinal parasite occurring in from 5% to 20% of the populace of this country, with an average over-all incidence of approximately 10%.<sup>11,45</sup> Extensive data have accumulated establishing the pathogenicity of this organism in man as well as in certain experimental animals.<sup>2,11</sup> The discrepancy between the incidence of infection and incidence of symptomatic amebiasis has not been clearly defined. It is felt by many that concomitant bacterial invasion is a prerequisite to symptomatic amebiasis, and, indeed, Craig thinks that all infestations are complicated by the presence of bacteria,<sup>11</sup> others that bacterial infection may lower the general resistance or facilitate entrance of the protozoan into the intestinal mucosa.<sup>5,35</sup> It is a prevalent concept that approximately 10% of the cases of amebiasis harbor organisms of the *Shigella* group.<sup>12</sup> In view of the frequency of non-specific symptoms, some workers have felt that the diagnosis of amebiasis should be made only in the presence of a complete therapeutic response to amebicidal drugs.<sup>39</sup>

For clinical purposes, the life cycle of *Endameba histolytica* is a relatively simple one, although detailed analysis of racial characteristics and related organisms makes its more definitive un-

derstanding somewhat intricate. It is felt that the most likely sequence of events is (1) ingestion of cystic form, which (2) excysts in the alkaline secretion of the small intestine with formation of metacysts which (3) by their cytolytic action invade the mucosa of the cecum from which (4) trophozoites further invade the submucosa or muscularis, occasionally the serosa, and may (5) be passed into the lumen to the more distal large bowel, where the process is repeated, or form typical amebic ulcers, and sometimes invade the venules or lymphatics, thus facilitating invasion of extra-intestinal organs.<sup>11,17,26</sup> Many local factors other than the bacterial ones mentioned above have been incriminated, including the total number of parasites, the pH of enteric secretions, the motility of the intestinal tract, the virulence of the parasitic strain, host-resistance, and others.<sup>17</sup> That symptomatic amebiasis occurs less commonly in children and more commonly in males and in the tropics has been established.<sup>11</sup>

**SYMPTOMS.** The symptomatology of amebiasis is protean. Many infected persons are entirely asymptomatic, the incidence ranging from 1.4%<sup>28</sup> to 61%,<sup>16</sup> although most observers place the incidence of asymptomatic carriers between these figures.<sup>2,11,25</sup> In this series, twenty cases (10%) were entirely free of symptoms which could be attributed to the presence of *Endameba histolytica*. The smaller number of symptom-free cases in this study is possibly attributable to the fact that these were all hospitalized patients, usually with symptoms referable to the gastro-intestinal tract.

Craig<sup>11</sup> classified symptomatic amebiasis into (1) carriers with indefinite gastro-intestinal symptoms, (2) recurrent attacks of diarrhea, (3) chronic amebic dysentery and (4) those with complications. In this series 4.4% were considered to be carriers with non-spe-

cific gastro-intestinal symptoms which included indigestion, flatulence, abdominal discomfort, constipation, eructation, malaise, fatigue, headache, etc. Of these, constipation was most common, occurring in 65% of the cases. The remaining cases were thought to have symptoms attributable to amebiasis.

No attempt was made to ascertain the incubation period in this group, but it has been said to be quite variable, ranging from several days to many months.<sup>26</sup> The onset was usually insidious, although in approximately 10% of the cases it was acute and explosive, in most cases in association with a more severe form of the disease. This figure is in accord with previous estimates.<sup>14</sup> The most common symptoms are tabulated in Table 1. It is immediately apparent that in this group of symptomatic amebiasis diarrhea is the paramount symptom, occurring in 58.6% of the cases. The categories of mild, moderate and severe are purely arbitrary, patients with from 5 to 10 bowel movements daily being considered moderate and comprising the majority of the group of those with bowel frequency. Alternate diarrhea and constipation, emphasized so strongly by some,<sup>2,17</sup> occurred in approximately 12.5% of these cases, and if combined with those patients manifesting diarrhea alone would create a figure of 71.1% or nearly 3 in 4 patients giving a history of diarrhea. Abdominal pain has been said to be present in 95.4%<sup>25</sup> of cases of amebiasis, though in this study its incidence was 53%. It was most frequently described as cramping, intermittent, not uncommonly generalized, but more usually occurring in the lower abdomen or in localized areas of the abdomen. The periodicity of these symptoms was striking, only 10% to 15% describing continuous pain or diarrhea.

The quality of the stool in the history varied markedly, some described by patients as not abnormal, others as

profuse watery diarrhea. Gross blood was described by 27.8% of this group. Mucoid stools were described by 20.4% of the patients. Other less common symptoms are depicted in Table 1. Fever was described by 11.2% of those cases which were not complicated by extra-intestinal forms of the disease (in contrast to the 55% of those with hepatitis or abscess), a figure approximating that of Karl and Sloan,<sup>25</sup> and supporting the statement of Klatskin<sup>28</sup> that slight temperature elevation is frequent, but that "high fever almost invariably indicated a complication". Futcher<sup>19</sup> thought that fever usually was present at onset, but Craig<sup>11</sup> has not found this to be true. Urticaria, reported in 40% of one group<sup>28</sup> was not observed in this series.

The duration of these symptoms varied greatly, but the great majority (71.4%) exceeded 6 months, a fact probably to some extent responsible for the frequency of persistent symptoms following adequate therapy (*vide infra*). Only 3.4% were of less than 1 week's duration and 14% had symptoms, usually intermittently, for greater than 10 years, the longest duration recorded being 27 years (2 cases).

Of interest is the fact that 4 cases were subjected to appendectomy (3 in this hospital, 1 elsewhere) because of doubt about the origin of abdominal pain. This is a not uncommon source of confusion, and Craig<sup>11</sup> thinks that "in every individual presenting symptoms of appendicitis an examination of the feces should be made, and if found (*Endameba histolytica*) anti-amebic therapy should be tried before surgical means unless symptoms are such as to demand immediate operation". In one series, a third of the cases of appendicitis coming to operation were found to have amebiasis,<sup>10</sup> and Faust<sup>41</sup> states that 10% of cases of appendicitis have amebic involvement. It should be emphasized that if response to anti-

amebic therapy in such cases is not prompt, surgical measures should be taken. Manson-Bahr,<sup>31</sup> in a large series of cases of amebiasis, found 5.4% coming to appendectomy and in none were *Endameba histolytica* found. Pathological examination of the appendices removed in this hospital showed no amebae, but treatment had been instituted in all cases prior to operation.

**PHYSICAL EXAMINATION.** It is a frequently emphasized fact that the most common physical finding in intestinal amebiasis is localized abdominal tenderness<sup>2,4,11,25,26,28,36</sup> usually about the cecum or sigmoid. In a large portion of this series the physical examination was entirely negative, although certainly the most common finding was abdominal tenderness, which was observed in 45% of the chronic cases and 65.5% of the acute; in the former, tenderness was most common in the right lower quadrant, although other areas, chiefly left lower quadrant and epigastrium, were frequently sensitive, and in the latter, generalized tenderness was usually observed. As has been shown by others<sup>11,36</sup> fever in the chronic cases is unusual, being found in only 2.9% of this series. Fever was observed in 50% of the acute cases, and whether this is due to secondary infection, as is believed by Craig,<sup>11</sup> or due to *Endameba histolytica* alone is impossible to state with assurance, although in no acute cases were pathogenic intestinal bacteria recovered, despite adequate bacteriologic study. That pyrexia frequently indicates a complication is evidenced by the fact that 66% of the cases of extra-intestinal amebiasis were febrile. Browne *et al.*<sup>7</sup> showed that fever occurred in 64% of complicated cases in contrast to 7.4% of uncomplicated ones. In 25% of the chronic cases in this series, thickened, easily palpable, sometimes tender colons were described. Craig's<sup>11</sup> statement that in every case in the chronic group weight

loss occurs is not borne out by the recorded observations in this group that 9% appeared chronically ill and another 3% showed evidence of weight loss. Actually the preservation of adequate gross nutrition was striking, despite prolonged bouts of moderately severe diarrhea in many instances.

Opinion concerning indications for, and significance of, sigmoidoscopic examination vary widely; in his monograph Craig<sup>11</sup> states that this procedure should be reserved for cases in which stool examinations are negative, and that of all cases examined, less than 25% reveal lesions. On the other hand, typical discrete ulcers have been reported to occur in from 21% to

discharge without fully developed ulcers; and 1 case was found to have a venous angioma in the sigmoid. In 8.2% of the proctoscoped cases the diagnosis of amebiasis was reached by the finding of *Endameba histolytica* in smears from the ulcerated areas, whereas in several of these cases repeated stool examination had previously been non-productive. The case in which the venous angioma was demonstrated suggests an additional reason for more frequent utilization of this procedure for the revelation of underlying lesions, such as carcinoma, polyps, lymphopathia venereum, and others, as well as facilitating the diagnosis of amebiasis.

TABLE I. SYMPTOMS IN UNCOMPLICATED INTESTINAL AMEBIASIS

PER CENT OF CASES			PER CENT OF CASES		
1	DIARRHEA - TOTAL	71.1	5	WEIGHT LOSS	14.6
	MILD	12.5	6	FEVER	11.2
	MODERATE	31.9	7	FLATULENCE	9.0
	SEVERE	14.2	8	CONSTIPATION	7.4
	ALTERNATING DIARRHIA AND CONSTIPATION	12.5	9	"INDIGESTION"	7.0
2	ABDOMINAL PAIN-TOTAL	53.0	10	ERUCTATION	6.9
	MILD	22.1	11	ABDOMINAL DISTENTION	6.2
	MODERATE	23.9	12	TENESMUS	5.0
	SEVERE	7.0	13	FECAL INCONTINENCE	2.0
3	STOOLS - GROSS BLOOD	27.8	14	SYSTEMIC ( HEADACHE, ANOREXIA, MALAISE, FATIGUE ETC	28.0
	MUCOUS	20.4			
4	NAUSEA AND VOMITING	16.5			

90% of cases,<sup>36</sup> approximately twice as often in symptomatic as in asymptomatic cases.<sup>35</sup> In contrast to Craig, Albright and Gordon,<sup>2</sup> feel that all cases should be proctoscoped. In this series, 61 patients were sigmoidoscoped and of these 37.7% revealed no abnormalities; those showing significant changes included: 21.3%, classical discrete undermined ulcers with normal intervening mucosa; 16.4%, diffuse hyperemia without visible ulceration; 11.0%, extensive involvement of the mucosa suggesting chronic ulcerative colitis; 10%, areas of spotty bleeding and mucoid

LABORATORY DATA. Of laboratory procedures, examination of the stool is the only method by which a definitive diagnosis can be established (exclusive of extraintestinal amebiasis). It cannot be overemphasized that great technical skill and prolonged training are prerequisites to adequate examination of stool specimens. No physician without at least 6 months' training in the definitive identification of this parasite should attempt to perform such examination. Numerous techniques have been utilized in isolating the protozoa, from simple unstained smears of

the stools to elaborate cultural methods. In this laboratory it is felt that a minimum of 6 stools should be examined, utilizing unstained smears or wet stains with Quensel's stain for trophozoites in loose stools and zinc sulfate flotation for cysts in formed stools. These preparations frequently need not be stained, but, if necessary, hematoxylin is adopted. Ameba cultures are reserved for those cases in whom several stool examinations are negative and in whom the disease is clinically suspected, or occasionally for confirmation of the diagnosis in the presence of cysts or trophozoites of uncertain nature; however, it is felt that *E. coli* may occasionally take on the characteristics of *E. histolytica* in culture and that the diagnosis should be made from direct stool examination whenever possible. Purging is recommended by some to facilitate diagnosis, and this procedure is utilized in this hospital after several negative stools are obtained and clinical suspicion persists. It must be remembered that purging may hinder the demonstration of the organism for several subsequent days.<sup>28</sup> A frequently overlooked fact is that, not uncommonly, previously administered barium or bismuth may temporarily eliminate *E. histolytica* from the stools.<sup>2</sup> Differentiation of the *E. histolytica* from other intestinal protozoa is beyond the scope of this paper, but the difficulty is obvious when one realizes that 32% of these cases had concomitant infestation with *E. coli*, *E. nana* or *Dientameba fragilis*.

Gross examination of the stool revealed that in 34% liquid or semi-liquid stools were passed by the patient on admission; the remainder were formed. Gross blood was observed in only 15 cases (8%), a figure considerably below the incidence described by the patients (*vide supra*), but tests for occult blood were positive in 20.5% of the cases. In the great majority of these

cases stool cultures for intestinal bacterial pathogens were performed, and in only 4 cases (2.3%) were the results productive, in contrast to the oft-quoted figure of 10% offered by others.<sup>2,12</sup>

Anemia (hematocrit below 36), thought to be common by Fitcher,<sup>19</sup> was found in only 5% of uncomplicated cases, although it occurred in 50% of those with complications. Likewise, leukocytosis exceeding 12,000 was present in only 5% of cases in whom it could be accounted for by no other means, though 65% of those with hepatic complications revealed a leukocytosis, usually with a shift to the left in the hemogram. Eleven cases (6.2%) demonstrated an otherwise inexplicable eosinophilia (greater than 10%), a fact that is in accord with other reports<sup>11</sup> in which the rarity of eosinophilia is encountered and with the statement that one must suspect co-incident infestation with helminths when this finding is noted.<sup>2</sup> Elevation of sedimentation rate was noted in 22% of uncomplicated cases in contrast to the statement of Klatskin<sup>28</sup> that this test is usually normal. In hepatic complications, sedimentation rate was elevated in 30% of cases, a figure considerably below the 81% quoted by Klatskin.<sup>28</sup>

The complement fixation test, found by Craig<sup>11</sup> to be highly specific, was employed in only 5 of these cases and in every case it was negative. This result lends support to the statements of others that with present technique incomplete reliance can be placed on this test.<sup>33,41</sup> When a more satisfactory antigen is available, this test should be a most useful instrument, as emphasized by Craig. Attempts to correlate agglutinations of *E. histolytica* cysts with infection have been unsuccessful,<sup>20</sup> and to date the complement fixation is the only serologic test of any degree of usefulness.

Barium enemata were carried out in 74 cases in this series. Of these 25



(34%) were entirely normal. The remaining 66% revealed abnormalities: (a) mucosal pattern, usually in the region of the cecum or sigmoid, although several revealed more extensive involvement, (b) 24% were reported as showing a "spastic colon"; (c) the remaining 9% revealed various evidences of abnormality, including polyposis, diverticulosis and chronic ulcerative colitis. The most characteristic Roentgen-ray changes are said to be cecal irregularity and deformity with incompetence of the ileocecal valve.<sup>36</sup> Incidence of abnormal findings have been variously recorded from 26%<sup>40</sup> to 100%<sup>40</sup> and our figure falls within this range. Craig<sup>11</sup> feels that barium enema cannot be accepted as of much value; but our experience in which 9% of the cases demonstrated other abnormalities of significance would lend support to the feeling expressed by Browne *et al.*<sup>7</sup> that (1) a negative barium enema is helpful in eliminating other diseases, (2) finding of typical changes tends to support the diagnosis and (3) finding of granulomatous changes which respond to anti-amebic therapy is "assuring". Roentgen-ray examination of the chest is almost universally accepted as being of value in cases of hepatic and pulmonary involvement<sup>11,27,41,45</sup> where changes ranging from elevation and fixation of the right diaphragm to extensive pleural and pulmonary involvement are observed. In this series, 80% of cases of hepatic involvement in which a chest roentgenograph was made revealed elevation and fixation of the right diaphragm with or without atelectasis in the right lower lobe, a figure approximating that of Sodeman and Lewis (81%).<sup>45</sup>

Other laboratory studies were of inconstant value. Abnormalities of the urine were found in 12% of cases with hepatic lesions (albuminuria, occasional hematuria, pyuria, cylindruria), but in only one intestinal amebiasis was al-

buminaria which was otherwise inexplicable encountered. Tests of liver function revealed significant abnormalities in 35% of those cases with liver involvement. Agglutinations for enteric pathogenic bacteria were positive in only 1 case, though performed in most, and 4 patients showed an unexplained monocytosis (11% to 16%). In no case were eosinophils reported in the stools, although Fletcher<sup>19</sup> reports that this finding was present "in many cases." Charcot-Leyden crystals are said to be suggestive of *E. histolytica*,<sup>11</sup> but were described in no case in this series.

COMPLICATIONS. *Endameba histolytica* is capable of invading practically all tissues and organs, but invasion occurs as secondary involvement to primary intestinal disease in the great majority of cases. Involvement of the liver is the most common of the more serious complications. The correlation between liver abscesses and *E. histolytica* was first pointed out by Councilman and Laflour,<sup>10</sup> but it remained for Rogers<sup>44</sup> to clarify the distinction between hepatitis and abscess formation. The protozoan may reach the liver by (a) direct extension from the bowel wall, (b) lymphatic spread or (c) via the portal vein, and after reaching this organ produces colliquative necrosis and disintegration with invasion of surrounding parenchyma by motile amebae.<sup>37</sup> Liver involvement occurs in from 22% to 55% of cases at autopsy, though clinically from 1.8% to 21% of cases of amebiasis have recognized hepatic lesions.<sup>11</sup> It is probable that many cases of hepatitis and abscess are unrecognized, since autopsy experiences indicate a significantly greater incidence,<sup>11,41</sup> though it must be said that many fatal cases of amebiasis occur on the basis of liver involvement. That hepatic manifestations may occur independently of gastro-intestinal symptoms is common knowledge, though by correlating clinical and autopsy evi-

dence of enteric disease Rogers<sup>44</sup> found that 96% of hepatic cases had concomitant intestinal amebiasis. The striking predominance of males (86.7%<sup>44</sup>) has never been adequately explained. A history of preceding diarrhea is obtained in from 25%<sup>48,50</sup> to 85%<sup>11</sup> and *E. histolytica* is found in the stool of 11% to 78%.<sup>37</sup> In one series approximately 50% had, clinically, abscess formation, the remaining being considered hepatitis.<sup>47</sup> In this series, 20 cases (10%) demonstrated liver involvement, and of these, 17 were considered hepatitis, 3 amebic abscesses; 75% of these cases were found to have *E. histolytica* in the stool, though frequently only after exhaustive search,

(84.5%), local pain in the region of the liver (75% to 100%), nausea and vomiting (22.1%), weakness, anorexia, and others (52.2%), jaundice (10.5%). In this group fever was present in 66%, pain in the region of the liver in 85% and jaundice in only 5%. The pain was frequently sudden in onset and exacerbated by respiratory effort. Its intensity varied with the duration, usually being more severe in the acute hepatitides, and continuous in most cases, irrespective of the duration. It is interesting to note that 4 cases (20%) had been treated prior to the development of hepatic complications with anti-amebic drugs, usually 6 months to 2 years prior to the development of hepatitis, yet these

TABLE 2. PHYSICAL FINDINGS IN UNCOMPLICATED INTESTINAL AMEBIASIS

ACUTE	ABDOMINAL TENDERNESS	CHRONIC
65.5%	TOTAL	45.0%
50.0%	GENERALIZED	9.0%
0.0%	LOCALIZED RLO	17.0%
16.5%	OTHERS	19.0%
16.5%	ABDOMINAL DISTENTION	5.0%
0.0%	UNDERNOURISHED, CHRONICALLY ILL	9.0%
16.5%	PALPABLE, THICKENED COLON	26.0%
50.0%	FEVER	2.9%

and 45% gave a history of antecedent diarrhea, one as long as 8 years prior to the development of hepatitis.

Klatskin<sup>27</sup> classifies amebiasis of the liver into (a) acute amebic liver abscess, (b) acute amebic hepatitis, (c) sub-acute amebic hepatitis, (d) chronic amebic hepatitis, (e) chronic amebic abscess, though in his series none of the latter were observed. In this series, there were 4 cases of acute hepatitis (20%), 6 cases of subacute hepatitis (35%), 5 cases of chronic hepatitis (25%), and 3 liver abscesses, all of which could be considered subacute. Ochsner and Debaquey<sup>37</sup> tabulate symptoms of amebic involvement of the liver as fever

cases were stool positive on admission to this hospital. Physical findings could be closely correlated with the symptoms, all of these cases appearing acutely or chronically ill, 85% revealing liver tenderness, and 80% hepatomegaly, (figures which approximate those offered by other observers)<sup>27,37</sup>. 35% showed signs of atelectasis, some with pleuritis, at the right lung base, and all were found to have splinted and elevated right diaphragms, frequently with bulging in the right lower interspaces. The frequency of pleurisy with or without effusion in association with amebic hepatitis has led Carruthers<sup>5</sup> to suggest that any patient demonstrating tender hepatomegaly, high diaphragm and

pleurisy warrants anti-amebic therapy. Amebic abscesses may rupture into the pleural cavity, parenchyma or bronchus of the lung, peritoneal cavity, pericardium, stomach, large or small bowel, lumbar muscle or skin, giving rise to the dire complications which are self apparent, though the prognosis after rupturing into a bronchus is less grave than that into a closed cavity.

Primary amebiasis of bronchi and lung has been said to occur,<sup>11,15</sup> but is secondary to hepatic disease. An almost universally fatal complication of amebiasis is metastatic involvement of the brain, which fortunately is rare, giving rise to symptoms and signs of a cerebral abscess. Two such cases were observed in this series (1% of the total), one of which died after extension into the meninges, with the development of a rapidly fatal meningitis, the second of which was a presumptive diagnosis, and unfortunately was not followed in this hospital.

Amebic granulomata are not uncommon and may simulate carcinoma of the large intestine,<sup>11,12</sup> sometimes causing intestinal obstruction, abscesses or perforation. These lesions may require surgical removal<sup>16</sup> and it is felt by some they may lead to malignant degeneration. Read and Anderson<sup>12</sup> report 4 cases in which carcinoma of the large intestine followed or accompanied amebic infection. In this series, 1 case of presumed amebic granuloma was seen and 4 cases of amebiasis in whom adenocarcinoma of the colon was found. Amebiasis may frequently involve the appendix, simulating acute appendicitis (*vide supra*), but may also simulate other causes of an acute surgical abdomen. One case in this series of amebic peritonitis was observed, although the primary site of involvement of the peritoneum was not ascertained. 21 of 24 peritonitides. This compli-

tion may arise from hepatic or intestinal invasion.

Other complications include perforation, massive intestinal hemorrhage, amebic cholecystitis, splenitis, urinary tract involvement, gastritis, enteritis,<sup>11</sup> arthritis,<sup>10</sup> prostatitis<sup>1</sup> and others, none of which were observed in this series.

The most common complication in this group was the development of chronic intestinal symptoms including chronic ulcerative colitis, regional enteritis, and others. Of this series of 205 cases, 88 were adequately followed after discharge from the hospital; however, 18 cases (8.8%) had persistence of symptoms while in the hospital, despite treatment which was successful in elimination of *E. histolytica* from the stools. Five patients in whom the picture of chronic ulcerative colitis was absent on the first admission, proceeded after therapy to develop the classical features of this disease, and another 7 had developed this syndrome prior to admission in a manner suggesting the possibility of an etiologic connection with amebic infection, giving a total of 12 cases (5.9%) in which chronic ulcerative colitis developed. Another group of 18 underwent a relapse following discharge and on readmission 5 were found to be stool positive; an additional 4 cases gave a history of adequate anti-amebic therapy elsewhere prior to admission to this hospital, and were found to be stool positive here. A total, therefore, of 52 cases, approximately 25% of the entire group of 205 cases, noted persistence or recurrence of severe intestinal symptoms (cases with persistent mild diarrhea were excluded) following what was assumed to be adequate therapy, although only 5 cases (2.9% of those who were actually given anti-amebic therapy) underwent stool positive relapse, or reinfection.

Diagnosis. The diagnosis should be suspected in all patients with intestinal symptoms; it is established, however,

only by (1) the finding by direct examination or culture of *Endameba histolytica* in the stool, urine, sputum, draining sinuses, etc., or from other tissues, or by (2) the emetin therapeutic trial in extra-intestinal involvement. The diagnosis can be strongly suspected in the presence of a positive complement fixation test, but the organism must be demonstrated for a definitive decision. The disease in which differential diagnosis is necessary most frequently is bacillary dysentery, and the accompanying table (Table 3) modified from Craig<sup>11</sup> outlines the essential differential features.

**TREATMENT.** Every case, irrespective of symptomatology, deserved adequate treatment,<sup>11,25</sup> in view of the known

of hepatitides) and in all cases of hepatitis, emetine therapy should be instituted prior to surgical procedures.<sup>3,27</sup> Opinion concerning its use in intestinal amebiasis is divided; some feel that emetine should never be used in uncomplicated intestinal disease,<sup>1,26</sup> though most observers feel that it is useful in alleviating the symptoms of acute amebiasis;<sup>7,13,18,28,45</sup> many feel that in view of the known tissue invasion in all cases, emetine should routinely be combined with iodine or arsenical compounds.<sup>2,13,25</sup> More recently emetine administered orally in enteric coated tablets has been found highly effective and free of significant toxic effects in a small series.<sup>16</sup> Emetine in combination with bismuth and

TABLE 3. DIFFERENTIAL DIAGNOSIS FROM BACILLARY DYSENTERY  
MODIFIED FROM CRAIG<sup>2</sup>

AMEBIC	BACILLARY
CHRONIC, ENDEMIC	ACUTE, EPIDEMIC
INCUBATION - DAYS TO YEARS	INCUBATION USUALLY < 1 WEEK
USUALLY INSIDIOUS ONSET	ACUTE ONSET
SYMPTOMS INTERMITTENT	CONTINUOUS, DURATION FEW DAYS
MAY DEVELOP HEPATIC INVOLVEMENT	LIVER RARELY INVOLVED
COLON THICKENED WITH LOCALIZED TENDERNESS	GENERALIZED ABDOMINAL TENDERNESS
MODERATE OR NO TENESMUS	SEVERE TENESMUS
RARE, IF ANY, ARTHRITIS	ASSOCIATED ARTHRITIS NOT UNCOMMON

tissue invasion and the possibility of serious complications. The treatment of choice remains somewhat problematic.

Since Rogers<sup>43</sup> hailed emetine as a specific curative agent in this disease three-and-a-half decades ago, this drug has probably been the most extensively used of the amebicides. It is a generally accepted fact that parenteral emetine acts largely on tissue forms and is not successful in eliminating intestinal amebae. That it is the drug of choice in extra-intestinal amebiasis is undisputed (although in a recent report, it was shown by Conan<sup>9</sup> that chloroquine was effective in curing all of a small series

iodine (EBI), has been found the most useful mediant by the British.<sup>1,19,31</sup> Emetine is a toxic drug, the action of which is cumulative and the frequency of untoward side effects is widely recognized, and, for that reason, it must be used with caution. *Endameba histolytica* has been shown to become resistant to emetine<sup>18,22</sup> and Manson-Bahr feels that the widespread use of emetine during the war years has been a major factor in producing refractory cases of amebiasis.<sup>31</sup> In this series, emetine alone was used in only 5 cases, 3 of whom had persistent diarrhea following treatment, and one of whom was not followed, although these

cases became, temporarily at least, stool negative. Eight cases gave a history of previous emetine therapy and were found here to be stool positive. No untoward effect was observed in any case treated with emetine except transient electrocardiographic changes in 2 cases and occasional local irritation.

The iodine-containing drugs, chiniofon, diodoquin and vioform have been found to be of great usefulness in treating uncomplicated amebiasis, iodine being a direct amebicide. That the iodine in the compounds is absorbed has been shown by the use of the radioactive element in chiniofon.<sup>4</sup> The therapeutic efficacy of these drugs ranges from 88 to 99%,<sup>12,15</sup> when used alone. The incidence of toxicity is negligible, except for occasional diarrhea observed with chiniofon (*per os*). Slight diarrhea was seen in 4 cases in this series who were treated with chiniofon, none in those treated with vioform or diodoquin. Accurate evaluation of their efficacy in this series is impossible since the great majority were combined with emetine or arsenicals, though no stool positive relapses were observed except in one case in which Yatren (chiniofon) was used by retention enema in combination with parenteral emetine.

Arsenic, likewise a direct amebicide, has been used in various forms in the treatment of amebiasis, but by far the most satisfactory, and least toxic form is carbarson, either orally or by retention enema. Satisfactory results have been obtained in from 75 to 95% of cases.<sup>11,17,18,12</sup> Faust<sup>17</sup> has found carbarson to be only 75% as efficacious as chiniofon and the greater incidence of toxic reactions must not be overlooked,<sup>21</sup> particularly in the presence of liver disease. It is felt by some that arsenical therapy in combination with iodoquinolinic medicaments is the most satisfactory mode of therapy.<sup>13</sup>

Combined therapy with several of

the above-mentioned drugs has been used in our series and the variations in the method have been so extensive that statistical studies of each combination would be insignificant. However, the overall results in elimination of the organism by utilizing several drugs have been gratifying (2.9% relapse), although not superior to that obtained in the small number of this series in which arsenical or iodoquinolinic therapy alone was used.

Many other drugs have been used in this disease including Kurchi-bark, emetineperiodine, amcmitine, chaparra argosa, bismuth sub-nitrate,<sup>11,31</sup> trilactic acid,<sup>49</sup> and penicillin,<sup>29</sup> but results have been inferior to date to those obtained with the more conventional drugs.

In view of the frequency of secondary bacterial invasion, it has been frequently suggested that sulfonamide and, or, penicillin (and we might add, streptomycin) be used,<sup>15,23,15</sup> and this seems to be based on logical reasoning. In this series, such therapy was used in no instance, although it is conceivable that in certain fulminating cases antibiotic or chemotherapeutic agents should be a useful adjunct to amebicidal therapy.

MORTALITY. In contrast to the mortality rate prior to the institution of modern therapy (Fletcher, 23.5%),<sup>19</sup> the prognosis is now regarded as excellent, usually depending on the basis of complications,<sup>11</sup> and, if early diagnosis and treatment are established, fatalities should practically be abolished. In this series, the total mortality was 3.3%, of which only 1.4% (3 cases) could be attributed to amebiasis. All cases were not followed adequately after treatment, and it is possible that the mortality might be somewhat higher. Of those deaths in which *E. histolytica* could be incriminated as the responsible agent, 1 died of liver abscess, complicated by cerebellar abscess and meningitis, 1 of persistent amebiasis

with severe chronic diarrhea not responding to repeated courses of amebicidal therapy and ileostomy, and 1 with the classical picture of regional enteritis. The remaining 4 deaths were due to Hodgkin's disease (one), teratoma (one), and adenocarcinoma of the colon (two). Autopsy was obtained in 6, all of whom had adequate antiamebic therapy, and no amebae were demonstrated in 5 although present in the case with the cerebellar abscess.

COMMENT. This analysis of 205 cases of proven amebiasis has reaffirmed previous reports in which the protean nature of the disease with its varying clinical course and frequent paucity of physical findings have been described. Diarrhea has been shown to be the foremost symptom and localized abdominal tenderness the most common physical finding. The incidence of complications has approximated the classical figures, that of hepatic involvement being foremost, and extension to the lungs, peritoneum, brain and elsewhere less common. The diagnosis is made on the basis of demonstration of *E. histolytica*, or a rapid therapeutic response to emetine. Treatment is probably best accomplished by the use of iodoquinoline compounds in uncomplicated amebiasis. Emetine should be reserved for severe dysentery (for symptomatic control), and extra-intestinal involvement, although one could not be condemned for combining emetine with arsenical or iodine compounds if so desired, and the combination of more than one drug is indicated in resistant cases. It cannot be overemphasized that all patients harboring the organism deserve adequate therapy, and all treated cases should be followed with serial stool studies and treatment reinstituted if relapse occurs. It appears that the feeling expressed by Adams<sup>1</sup> that the actual preparation of drugs is less important than the period of time over which a

number of drugs is given can be supported.

That certain cases of amebiasis become intractable to all therapy has long been recognized,<sup>1,6,11</sup> and in this series one patient died of what seemed to be intractable amebic disease. On the other hand, the persistence of diarrhea, abdominal pain and other symptoms suggestive of the persistence of amebiasis, in the absence of demonstrable protozoa in the stools, has likewise been frequently catalogued.<sup>2,11,13</sup> In this latter group, it may sometimes be difficult or impossible to distinguish the postamebic intestinal changes, from the co-incidental occurrence of amebic infection in patients with spastic or mucous colitis or chronic non-specific ulcerative colitis. The most striking result of this study is the fact that in 25% of the cases, gastro-intestinal symptoms of moderate to severe degree persisted after what is assumed to be adequate therapy, and that of these 5.9% developed or had developed the features considered diagnostic of chronic ulcerative colitis, namely, proctoscopic and Roentgen-ray changes with persistent chronic bloody diarrhea.

The high incidence of infection in asymptomatic carriers engenders doubt in the minds of some that the chronic diarrhea seen after eradication of the organism is the result of its presence previously in the tissues,<sup>39</sup> and others feel that "many patients become bowel invalids because of a neurogenic tendency."<sup>4</sup> That amebiasis may result in chronic ulcerative colitis has been previously shown<sup>6,13,45</sup> and it has been suggested that all cases of chronic ulcerative colitis be given a trial of antiamebic therapy.<sup>36</sup> In one group of 140 cases, 29.1% demonstrated persistence of diarrhea in the presence of negative stools, a figure approximating the 25% of this series. Craig<sup>11</sup> emphasizes the fact that single attacks of amebiasis usually show no complication compar-

able to this, whereas "frequently" those persons with repeated attacks develop chronic diarrhea which . . . "may imitate sprue." Howard<sup>21</sup> found that 73% of a small series of ameba "carriers" underwent symptomatic relapse after adequate therapy.

The difficulty involved in clearly distinguishing those cases of "spastic colon" with concomitant amebic infestation from the cases in which irreversible intestinal changes have developed on the basis of amebic activity is apparent. That post-amebic colitis exists is not disputed, but that careful study is necessary to establish its presence is emphasized. Careful scrutiny of the histories of those patients who had developed by the time of admission, or subsequently developed, chronic ulcerative colitis reveals evidence that in at least 9 of the 12 cases, the history and physical findings, correlated with the original proctoscopic examination, strongly suggest an amebic pathogenesis of the chronic disease of the colon wall. In 3 cases the evidence was equivocal. The majority of cases demonstrated temporary improvement in symptoms and in proctoscopic findings coincident with anti-amebic therapy, only to relapse at a later date without evidence of *E. histolytica* in the stools.

Of the remaining 19.1% of our patients, in whom abnormal intestinal symptoms persisted, usually intermittent diarrhea and abdominal pain, many have received subsequent courses of amebicidal drugs, frequently with temporary improvement, though symptomatic relapse was forthcoming, and in these patients proctoscopy revealed either normal mucosa or diffuse hyperemia. Nine cases (4.4%) had disease of the large intestine which could account, at least in part, for the symptoms: 5 diverticulosis, 1 polyposis; but the remainder had no evidence demonstrable of other disease processes. Further therapy was notably unsatis-

factory in this group. In 16% of the group with persistent symptoms, it was felt that a large personality element was involved, and the patients were discharged with diagnoses of "gastro-intestinal neurosis," "spastic gastro-intestinal tract," and the like, although symptoms referable to the gastro-intestinal tract prior to the onset of symptoms which suggested amebiasis were usually absent. Unfortunately, definitive personality studies were not carried out in the great majority of these patients.

The fact that 25% of the patients seen in this hospital in whom amebiasis was diagnosed continued to have symptoms after treatment demands that, in the future, careful study of personality, large bowel mucosa, and therapeutic response be made in all cases harboring this parasite. Follow-up studies must be cautious and prolonged, and therapy reinstituted in the presence of a relapse. Care must be taken to avoid over-treatment with emetine and to provide proper general medical and hygienic care with special emphasis on avoiding the "bowel consciousness" attendant on the development of such a disease, and psychiatric therapy instituted when necessary, though it seems probable from this study that the personality factors are less prominent in persistent post-amebic diarrhea than has been emphasized by some.

SUMMARY. 1. The 205 cases of proven amebiasis seen in The Johns Hopkins Hospital in the period extending from 1936 to 1946 inclusive have been reported.

2. The symptoms, physical findings and laboratory data have agreed relatively closely with those previously described.

3. The incidence of post-amebic stool-negative diarrhea has been shown to be 25% and the total incidence of development of chronic ulcerative colitis to be 5.9%.

4. More careful case analysis and follow-up studies in large series of patients with amebiasis are encouraged.

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# SUBACUTE THYROIDITIS, STRUMA FIBROSA, STRUMA LYMPHOMATOSA: A CLINICAL-PATHOLOGICAL STUDY

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THE subject of non-suppurative thyroiditis has been of interest mainly to the surgeon and pathologist because the diagnosis has usually been made only at the operating table or in the pathologist's laboratory. Indeed no necessity for distinguishing between the various forms existed since the therapy for all forms of thyroiditis was the same; *i.e.* thyroidectomy. We believe that it is possible to distinguish one group of cases—subacute thyroiditis—in which the diagnosis can be made preoperatively with reasonable certainty and in which operation may not be necessary.

Cases of non-suppurative, nonspecific thyroiditis have been broadly classified into Hashimoto's struma (struma lymphomatosa) and Riedel's struma (struma fibrosa) after the two men who first carefully described the pathological and clinical manifestations of the respective conditions. Generally included in with the struma fibrosa group, either as a recognized named variant or not, is a third group of cases, first studied in detail by DeQuervain<sup>5</sup> in 1904 and carefully reviewed and classified by him in 1936.<sup>6</sup> This group has been variously titled subacute thyroiditis, giant cell thyroiditis or pseudo-tuberculous thyroiditis according to whatever characteristic impressed the particular pathologist reviewing the slides. It is this last group of cases that we believe forms a distinct patho-

logical and clinical entity, and is not merely a stage in the formation of an eventual struma fibrosa. This view was expressed originally by DeQuervain<sup>6</sup> and more recently by Crile.<sup>3</sup>

A word of historical clarification might be in order concerning Riedel's struma. In 1896 and 1897 Riedel<sup>22,23</sup> described 3 cases of "iron hard" thyroid enlargement which he wished to distinguish from carcinoma. Following thereafter other similar cases were reported by Tailhefer,<sup>29</sup> Silatschek,<sup>27</sup> Spannos<sup>28</sup> and Carle.<sup>12</sup>

When therefore in 1910 Riedel<sup>24</sup> presented a 15 year follow-up of 1 of his original cases he could describe a typical case as one occurring in a young individual who would present signs of a subacute enlargement, and induration of the thyroid accompanied by severe dyspnea. Duration of symptoms was short; 6 weeks, 8 to 10 weeks and 6 months in the 3 original cases. All patients were afebrile and all goiters were non-tender.

The original microscopic descriptions were not very detailed, mentioning only an accumulation of round cells and spindle cells which appeared to crowd out the normal follicles, a slight endarteritis and a rapid growth of young connective tissue. From this, it is quite apparent that he did not describe the painful, febrile type of thyroid enlargement which characterizes subacute thyroiditis. If we wish to be

accurate in our classification, we should limit the term Reidel's struma to those cases conforming most closely to the clinical and pathological description mentioned, with the realization that many unrelated conditions will be included until discovery of etiological factors makes classification more rational.

In 1912 Hashimoto<sup>11</sup> described another form of diffuse enlargement of the thyroid gland characterized microscopically by diffuse lymphocytic infiltration and destruction of acinar elements. He distinguished this condi-

Eckerson,<sup>2</sup> McClintock and Wright,<sup>20</sup> Lee,<sup>16</sup> McSwain and Moore,<sup>21</sup> Graham,<sup>10</sup> Crile,<sup>3</sup> Schilling<sup>25</sup> and Marshall<sup>18</sup> have thrown the balance of opinion in favor of this later view. Particularly convincing is the fact that several authors<sup>2,14,20,25</sup> have reported cases of struma lymphomatosa, with further operation after intervals up to 4 years in which the microscopic picture underwent little or no change. However, it must be admitted that some glands are encountered which have characteristics of both conditions and suggest that a borderland between the struma lymphomatosa and fibrosa

TABLE I. -- SUBACUTE THYROIDITIS

Microscopic Pathology

	Type of Involvement	Tubercles	Giant Cells	Fibrosis	Lymph follicles with germinal centers	<u>Infiltration</u>	
						Lymphocytes & Plasma cells	Polys
M.R.	D	Numerous	Numerous	Dense	0	Numerous	2+
M.M.	D	Numerous	Numerous	Dense	0	Numerous	3+
*C.G.	D	Moderate	Moderate	Dense	0	Numerous	1+
G.J.	D	Numerous	Moderate	Dense	occ.	Numerous	0
**S.N.	L	Numerous	Numerous	Mod. dense	0	Numerous	3+
M.L.	L	Numerous	Numerous	Dense	occ.	Numerous	2+
D.H.	D	Numerous	Numerous	Dense	0	Numerous	3+
S.G.	D	Numerous	Numerous	Dense	0	Numerous	4+

D = Diffuse

L = Localized

\*Small adenoma present

\*\*Colloid adenoma present

tion from the specific thyroiditis, syphilitic, tuberculous, et cetera, and also from Riedel's struma.

Ewing<sup>8</sup> in 1922 expressed the opinion that Riedel and Hashimoto had described different stages of the same disease. This view held sway until Graham<sup>9</sup> in 1931 reviewed the 104 reported cases that could be found and by contrasting the clinical courses concluded that the two conditions were clinically and pathologically distinct. Since then reviews by Joll,<sup>11</sup> Clute and

may exist. Graham<sup>10</sup> in 1940 stated that "the microscopical findings alone are not sufficient to distinguish between Hashimoto and Riedel's or between these and certain cases of exophthalmic goiter, chronic inflammation, degeneration and fibrous replacement in and around adenomata and involutional changes in senility."

From 1595 thyroidectomies performed in the past 8 years, we have selected 24 cases of non-specific thyroiditis and find that they follow the

following 3 subgroups: Pseudotuberculous subacute thyroiditis, struma fibrosa and struma lymphomatosa. An illustrative example of each is presented.

**PSEUDOTUBERCULOUS, SUBACUTE THYROIDITIS—8 CASES, INCIDENCE 0.5%.**

*Clinical Characteristics.* These patients usually have no previous history of thyroid dysfunction or of any other endocrine disorder. The age range is wide, from 10 to 65 years, in the cases of DeQuervain, the largest number occurring in the second to fourth decades.

rynix or referred to the ear, was the outstanding symptom in all cases and in 6 of the 8 cases was the initial symptom. Associated with the pain was a tender enlargement of the thyroid, either diffuse or localized, and symptoms of tracheal pressure such as hoarseness, cough, choking sensations, pain on swallowing and dysphagia. Fever, at some time during the course of the illness, appeared as the most common sign of systemic disease, being present in 6 cases. Of the 6 febrile

TABLE 11 - ANALYSIS OF 24 CASES OF NON-SPECIFIC THYROIDITIS

Cases	Subacute Thyroiditis	Biedel's Struma	Hashimoto's Struma
	8	7	9
Age Range	36-61 years. Average 43 years	37-53 years. Average 46 years	6-53 yrs. Average 38 yrs
Post Menopausal	2 cases	5 cases	3 cases
Symptoms Duration	2 weeks to 1 year	6 weeks to 3½ months	2 months to 20 years
Thyroid enlargement	Moderate in size, invariably tender	Relatively rapid growth, non-tender and bulky	Slow growing, bulky and non-tender
Pain	Present and severe in almost all cases	Absent in all cases	Absent in all cases
Tracheal pressure	Present in some form in all cases and moderate	Present in only 2 cases	Present in 1 case
Fever	Present at some time in almost all cases	Absent in all cases	Absent in all cases
Weight Loss	Present in the majority of cases, usually 10-12 lbs	Present in only 1 case	Present in only 1 case
Preoperative thyroid dysfunction	Hyperthyroidism in 1 case	Hypothyroidism in 2 cases	Absent
Signs	Firm, or hard, tender, bilateral enlargement, 2-3 x normal size	Firm, hard, nodular, bilateral, non-tender enlargement	Firm, bilateral, non-tender enlargement
Laboratory Data	Sedimentation rates elevated. PBI elevated moderately. Low serum cholesterols	Low PBI's in 2 cases	No abnormalities
Operative Findings	Gland usually adherent to muscles, friable and poorly vascularized	Gland usually deeply fixed to surrounding muscles, firm fibrous and avascular	Firm, nonadherent gland
Pathology	Average amount of tissue removed 24 gm. Dense cellular connective tissue. Well formed tubercles with giant cells and histiocytes and small round cells. Clusters of polymorphonuclears.	Average amount of tissue removed 42 gm. Massive destruction of thyroid acini. Increase of interacinar connective tissue. Dense plasma cell and round cell infiltration	Average amount of tissue removed 57.7 gm. Diffuse, dense infiltration by lymphocytes with numerous follicles. Marked acidophilic degeneration of acinar cells
Therapy	Thiouracil derivatives, x-ray therapy Thyroidectomy	Conservative thyroidectomy	Subtotal thyroidectomy

Our cases in this group range from 36 to 61 years, averaging 43 years. Females predominate in this series 7 to 1. Crile's<sup>3</sup> cases showed a 6:1 ratio and DeQuervain's a 2:1 female-male ratio. Only 2 of the women were postmenopausal, surgically induced in both. Four of the women had had pregnancies in the past. Symptoms of local and systemic disease were present though the former predominated. Pain, in the thyroid region of the neck or in the pha-

cases, the pyrexia was present at the onset, in 3 cases, and 4 were febrile at the time of operation. Nothing characteristic was found in the temperature curve. One patient ran a spiking temperature to 104 daily, others stayed consistently at 101 to 102. Duration of fever was from 2 days to 8 weeks. A significant weight loss of 10 to 12 lbs. was noted in 5 cases. Only one patient presented clinical evidence of hyperthyroidism including nervousness, pal-

pitiation, tremor and heat intolerance, which preceded the onset of fever by several weeks. The details are given later in Case 1. The duration of symptoms ranged from 2 weeks to 1 year, with 6 cases less than 2 months.

At physical examination, the thyroid was usually found to be enlarged 2 to 3 times the normal size, either firm or stony hard, and invariably tender. Bilateral involvement was apparent in 6 of the 8 cases. No enlarged cervical lymph glands were ever palpated. In only 1 case was the trachea clinically

At operation the glands encountered were pale gray and very hard. Some were described as woody and others as stony hard or cartilaginous in consistency. In 5 of the cases, the thyroid was adherent to surrounding muscles. In 4 cases the gland was described as friable or brittle and in 3 cases poor vascularity was commented upon. A bilateral subtotal thyroidectomy was done in all but 1 case. The postoperative course was invariably uneventful. Follow up examinations were unfortunately not obtainable.



FIG. 1 A.—Subacute Thyroiditis: A typical tubercle consisting of a surrounding zone of round cells and dense connective tissue and several multinucleate giant cells radially arranged about a central drop of colloid (X 84).

deviated from the midline. In one other case, the skin of the neck was red and warm. Laboratory data yielded little valuable information. Sedimentation rates, when done, were markedly elevated. White counts were slightly increased. Four patients who were febrile during hospitalization had elevated BMR's of +7, +24, +30 and +55. Serum cholesterol determinations in those 4 cases were 132, 174, 141 and 141 per 100 cc. respectively. Kline tests when done were negative.

*Etiology:* The etiology of the disease is completely obscure. The work of the past is difficult to unravel since the condition when encountered clinically and allowed to subside spontaneously has been called acute or subacute non-suppurative thyroiditis. Yet the same syndrome when operated upon has been called Riedel's disease. Thus DeCourcy<sup>4</sup> in discussing the role of perithyroiditis in the etiology of what he supposed to be Riedel's struma was actually studying 2 cases of non-sup-

purative thyroiditis. Crile,<sup>3</sup> on the other hand, demonstrated by biopsy his view that the two conditions were identical. All attempts to isolate a bacterial agent have been unsuccessful. Blood cultures during the acute stage of 1 of our cases were uniformly negative. It is also hardly conceivable that a febrile condition going on for weeks to months could be due to a reaction of the gland to direct invasion or toxic effects of the ordinary bacteria of the nasopharynx, as maintained by Schilling.<sup>25</sup> Sufficient numbers of cases have been treated with penicillin and sulfadiazine, in

*Pathology and Pathogenesis:* Grossly, the gland appears to be uniformly involved and to be firm in consistency, grey white or pale brown in color and dense white fibrous strands can be seen traversing the cut surface. The average amount of tissue removed in the bilateral subtotal operations was 24 gm.

On microscopic examination, the following features are apparent:

(1) A dense, young, cellular, connective tissue proliferation circumscribing the lobules and separating them widely.

(2) Destruction and degeneration of

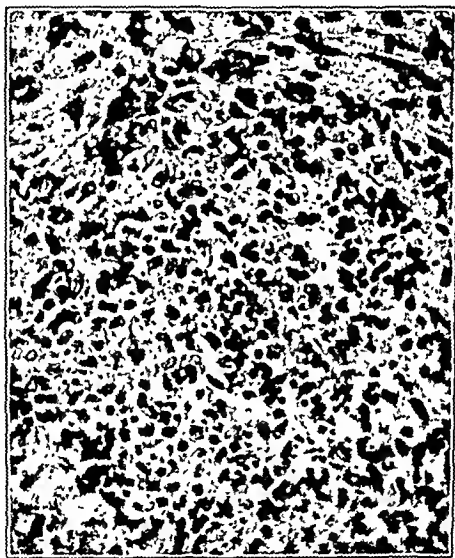


FIG. 1 B.—Subacute Thyroiditis: An area with numerous well preserved and degenerated polymorphonuclear leukocytes (X 322).

doses adequate to control the bacteria of the respiratory tract, without affecting this syndrome, to make it unlikely that these bacteria are the etiological agents. No virus work has been done. Tuberculosis and syphilis are effectively eliminated as etiological agents by the uniform absence of tubercle bacilli and negative serological studies. The entire syndrome and pathological picture seems to suggest an acute inflammatory reaction rather than a degenerative one.

thyroid acini with the formation of tubercles containing giant cells which appear to be phagocytosing a central drop of colloid.

(3) A moderately dense inflammatory infiltration of the interstitial tissue by small round cells, mononuclear cells and plasma cells.

(4) A scattered, focal accumulation of fresh and degenerated polymorphonuclear leukocytes found centered in tubercles and in and around degener-

ated thyroid acini. This was found in all cases but 1.

(5) Many lobules of thyroid acini which contain colloid and appear to be completely uninvolved.

From these features it is apparent that all parts of the gland are not involved equally or simultaneously. It would seem, then, that the destructive or inflammatory forces do not act at one time, but rather continue to pro-

point serves as a focus for entry of tissue histiocytes which can be seen entering in large numbers from the fibrous tissue. These histiocytes appear singly to phagocytose colloid. In other follicles, the entire lining epithelium is degenerated and desquamated into the center of the follicle and large numbers of histiocytes enter and coalesce to form radially arranged giant cells. These tubercles form a characteristic

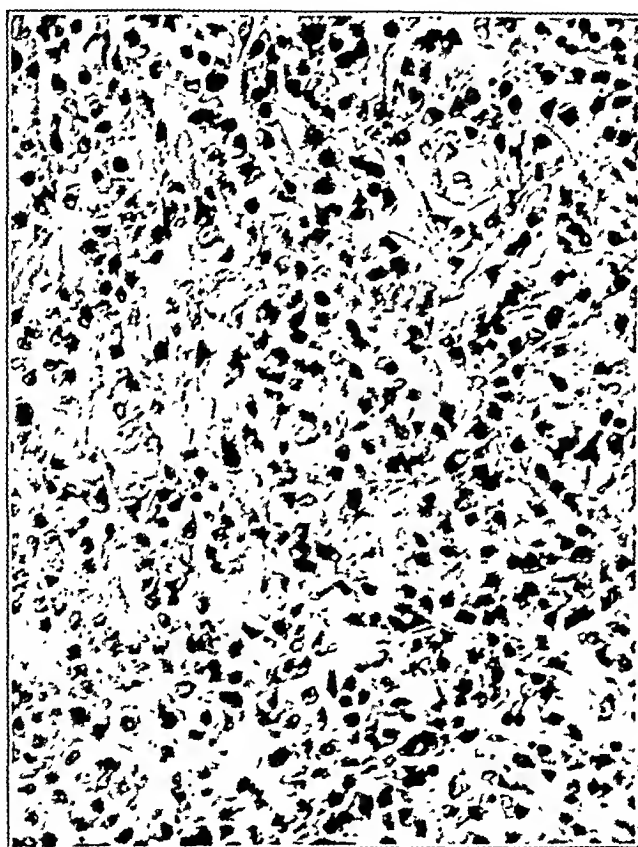


FIG. 2.—Riedel's struma: Plasma cell and lymphocytic infiltration, massive destruction of acini and pronounced increase in collagenous tissue (X 322).

duce changes during the entire course of the disease. It is our belief that the initial inflammatory process begins in the interstitial tissue surrounding those thyroid acini which are at the periphery of the lobule. Monocytes and small round cells infiltrate the follicle wall and lodge in the colloid. Study of serial sections reveals that at some point a breach in the wall is made and the lining epithelium is destroyed. This

lesion of the disease. Clusters of polymorphonuclear leukocytes are found inside and around some of the tubercles. No other form of thyroiditis presents a clearly formed tubercle. In the healing stage the colloid disappears from the center of the tubercle and it undergoes fibrous organization.

*Therapy:* The tendency of this disease is toward spontaneous remission. However, the course may be a matter

of months and be quite uncomfortable. The use of thiouracil and Roentgen-rays<sup>3,22</sup> has seemed to shorten the course and these are probably the treatment of choice. Crile<sup>3</sup> reports that 600 to 800 Roentgens to the neck effect a complete remission in a few weeks and that pain and temperature subside in a few days.

**CASE C. G.,** 36 year old white female. *Present Illness:* About 1 month before admission the patient noted increasing nervousness,

blood pressure 120/60, pulse 120, respiration 20. The patient was thin and agitated. No ocular signs of hyperthyroidism were present. The trachea was in the midline. The thyroid was visibly enlarged, tender, stony hard and 2 to 3 times normal size. No other unusual physical findings were apparent.

*Course:* The patient ran a persistent fever of 101 degrees and penicillin 400,000 units daily was given intramuscularly every 3 hours for 1 week. This produced no apparent effect on the process. Lugols 10 mm., 4 times a day was given concomitantly without noticeable effect. The laboratory data showed Kline



FIG. 3.—Hashimoto's struma: Showing the diffuse nature of the lymphocytic infiltration, the small size of the acini, and the hypertrophy of the lining cells. One large lymph follicle with a germinal center is seen (X 84).

palpitation, tremor of the hands and marked intolerance to heat. A choking sensation and a swelling of the anterior aspect of the neck were noted. Menses became irregular. She lost about 15 pounds. Two weeks later she began to feel an exquisitely tender swelling of the thyroid and marked pain on swallowing. A persistent diarrhea began and she became febrile with spikes of temperature to 102 daily.

*Personal History:* Unmarried, no illnesses other than childhood diseases. One sister had a toxic goiter.

*Physical Examination:* Temperature 101,

test negative. Sugar 94 mg. per 100 cc., Total Cholesterol 141 mg., 24% free. Total Protein 8.0 gm.%. Albumin 4.4, Globulin 3.6 gm.%. Blood culture—sterile. Hb 80%, WBC 7,700 (Polys. 68%, Lys. 28, Monos. 1%, Eos. 2, Bas. 1), Urine neg. Sedimentation rate 80 mm./hr. Chest x-ray negative. ECG—sinus tachycardia, right axis deviation. BMR +30% on admission and +16% after 1 week of bed rest. A bilateral subtotal thyroidectomy was performed while the patient was febrile, her postoperative course was smooth and she became afebrile 2 days later.

*Operative Findings:* A gland, diffusely en-

larged to 3 times normal size, very friable, firm and grey white was found. The histopathology is shown in Figure 1.

**RIEDEL'S STRUMA (STRUMA FIBROSA).** 7 cases. Incidence 0.44%. *Clinical Characteristics:* These cases all presented a picture of painless, relatively rapid, bulky, thyroid enlargement. The average duration of symptoms was 1.8 months, varying from 6 weeks to 3½ months. All patients were women, though this is not the usual rule and 2 of Riedel's cases were men. The average was 46 years. Six of the women had had 1 or more pregnancies and 5 of them were beyond the menopause. In only 1 patient did this struma develop on the basis of a pre-existing symptomless goiter. This duration is considerably shorter than other reports,<sup>3,7,16</sup> and may account for the fact that very few of our cases exhibited the severe dyspnea or choking sensations of Riedel's original cases. Only 1 patient complained of difficulty with deglutition and a sensation of tracheal pressure. Two patients were clearly in an early phase of hypofunction, which though not clinically apparent presented itself through low BMR's, low voltage ECG's with iso-electric T waves and an elevated serum cholesterol.

On physical examination, all the glands were described as firm or hard and many felt nodular. Involvement was usually more prominent on one side or another. Laboratory examination except in the hypothyroid cases was noncontributory.

Since these symptoms and signs are not distinctive, the diagnosis is not frequently made preoperatively. Actually the differential diagnosis between this struma and carcinoma is so tenuous, that operation is mandatory.

At operation, the glands were found to be firm, fibrous, avascular, and two were deeply fixed to the surrounding

structures. Subtotal thyroidectomies were done in all 7 cases.

*Pathology:* The average amount of tissue removed was 42 gm. varying from 27 to 56 gm. The specimens appeared to be pale brown or grey, firm and fibrous.

All glands were diffusely involved and approximately to the same degree, though varying widely among each other. The outstanding features were: 1, A dense, diffuse plasma cell and lymphocytic infiltration. 2, Massive destruction of thyroid acini with virtual disappearance of all colloid and an acidophilic swelling and degeneration of acinar epithelium. 3, A pronounced increase in fibrous tissue mainly of a coarse interacinar type. Giant cells were found in several cases but these were not in the form of tubercles and were usually found in the lumina of acini with an intact lining epithelium. There were no clearly distinctive pathological features uniting all cases in this group just as Riedel's original cases were not homogeneous.

*Etiology:* Jaffe<sup>13</sup> in 1937 reported 4 autopsy cases in which a dense lymphocytic infiltration, a varying degree of fine and coarse fibrosis, absent colloid and desquamation of lining epithelium was noted in the thyroid. The cases were all women who had undergone long and debilitating diseases. He also reviewed cases of Addison's disease and found an associated dense lymphocytic infiltration and fibrosis of the thyroid in 4 of 11 cases. Womach<sup>30</sup> also noted that pathological changes similar to those described by Riedel may be associated with adrenal cortical insufficiency. However, none of our cases exhibited any evidence of a pluriglandular disorder or of a concomitant debilitating disease.

In view of the clinical course it does not seem as though this clinico-pathological picture is the end stage of a process which has first gone through



the stage of what is recognized as struma lymphomatosa. That the processes producing the two syndromes may be basically similar and only different in degree remains a possibility.

**Therapy:** It is generally agreed that thyroidectomy is the treatment of choice and that only as much tissue should be removed as is necessary to relieve tracheal compression and reduce the bulk of the tumor.

**CASE I. R.,** 49 year old white female. **Present illness:** This patient presented a history of some  $3\frac{1}{2}$  months of progressive, painless rapid enlargement of the thyroid with cough, hoarseness and choking sensations. There was no weight loss and none of the signs of hyper or hypothyroid activity were manifested.

**Past History:** Unmarried, post menopausal for 10 mo. Had been treated for a stomach "ulcer" for 2 years.

**Physical Examination:** Blood pressure 100/70, pulse 72, temperature 98. The thyroid was diffusely enlarged, 4 times normal size, moderately firm and somewhat nodular. There were no other significant physical findings.

**Course:** The diagnosis was Riedel's struma. Kline test negative. Blood sugar 74 mg. per 100 cc., Urea 14.8 mg., Cholesterol 311 mg., Hb 59%, WBC 8000 (polys. 69%, lys. 29, Monos. 2), Sedimentation rate 69 mm/hr. ECG low voltage. P-R interval 0.24 secs. BMR-17%. A subtotal thyroidectomy was done, the post operative course was smooth and uneventful.

**Operative Findings:** Diffusely enlarged, firm, adherent gland. Right lobe  $4\frac{1}{2}$  times normal size. The left lobe was 3 times normal size and extended around the trachea and compressed it.

**Pathology:** The specimen consisted of 2 portions of thyroid gland weighing 56 gm. The consistency was firm and hard. The cut surface was pale gray-brown.

**Microscopic:** The acini were small, irregular in shape and were lined by large polygonal cells with a granular eosinophilic cytoplasm and irregularly shaped large, vesicular nuclei. Little colloid was present. Multiple nucleated giant cells in moderate numbers were seen, but no tubercle formation was present. There was a diffuse, dense infiltration of the parenchyma by small round cells and plasma cells. Large lymph follicles with true germinal centers were seen. There was a marked increase in the interacinar and in-

terlobular connective tissue which was coarse and deeply eosinophilic. Figure 2.

**Comment.** This case illustrates the massive destruction of functioning thyroid tissue that can occur in this condition in a matter of a few months. Though she did not present symptoms of myxedema, the low voltage ECG, elevated cholesterol and low BMR, indicated the presence of early hypofunction.

**HASHIMOTO'S STRUMA (STRUMA LYMPHOMATOSA)** 9 cases. Incidence 0.56%.

**Clinical Characteristics:** The average age of these patients, all females, was 38 years. The youngest was 6 years of age at the onset of the disease and to our knowledge is the youngest reported case. This case is reported in detail. Joll<sup>14</sup> in his exhaustive study of the subject in 1939 found one case in a child of 10 years. Schilling<sup>25</sup> reported a case in an adolescent female of 15 years of age. At the other end of the scale, Joll's oldest case was 74 years old, but the majority of cases fall in the 3rd to 6th decades. Six of our cases had multiple pregnancies, 3 were post menopausal, 5 were not and the child showed no evidence of endocrine abnormalities. The chief complaint in all cases was a painless, slow-growing enlargement of the thyroid. Duration of this growth ranged from 2 months to 20 years, with a mean duration of 2 years. In 4 cases, nervousness was also recorded as an outstanding symptom. Only 1 case exhibited symptoms of tracheal pressure including hoarseness and dysphagia. Preoperatively, a right recurrent laryngeal palsy was found. This is in contrast to the findings of McSwain and Moore<sup>21</sup> in whose cases pressure symptoms of one type or another were almost uniformly present. No patients were myxedematous preoperatively. Follow-up examinations were obtained in only 1 case, the child, and she showed signs of myxedema and required thyroid extract. It is the general

consensus of all reviewers that about 40 to 60% of these patients will require thyroid extract postoperatively.

*Physical examination* revealed only a somewhat firm, bilateral thyroid enlargement. Laboratory examinations revealed a serum cholesterol in the high normal range in the 4 cases in which it was performed. Basal metabolic rates were within normal limits, but were done in only 4 cases. Blood counts did not reveal any relative lymphocytosis.

*Operative findings* consisted of an enlarged, somewhat firm gland. Only 1 gland was noted to be adherent to muscles and this was one to which Roentgen-ray therapy had been given 3 months preoperatively. In 1 other case, the trachea was noted to be angulated and narrowed. A subtotal thyroidectomy was performed in all cases but one in whom a total removal was effected.

*Pathology:* The amount of tissue removed averaged 57.7 gm. ranging from 11.5 to 138 gm. The tissue appeared firm grey or pale-brown and homogeneous. On microscopic examination, the presence of all the following characteristics were used in selecting cases.

1. Diffuse involvement of the entire gland to the same extent everywhere.

2. A dense infiltration with lymphocytes spread diffusely throughout the parenchyma and also found in focal collections with true germinal centers.

3. A marked swelling of the acinar lining cells in which granular, eosinophilic cytoplasm and large, hypochromatic nuclei are noted.

4. Small acini with slit-like lumina containing almost no colloid.

5. Very little or no increase in fibrous tissue.

*Etiology:* The only experimental approach was that of McCarrison<sup>19</sup> who claimed to have produced, in rats, a microscopic picture resembling struma lymphomatosa of humans by feeding a diet deficient in vitamins (wheat,

meat residue, olive oil and potassium iodide). The work has never been confirmed or expanded. It is interesting to note that the peculiar acidophilic degeneration of the acinar cells resembles closely the changes produced by thiouracil.<sup>1,17,20</sup>

*Therapy:* Roentgen ray therapy has caused some moderate degree of resolution of the tumor in many cases. However, thyroidectomy appears to be more satisfactory and a conservative removal is indicated.

CASE C. F., 7½ years old white female. *Present Illness:* for 1½ years a progressive swelling of the base of the neck was noticed by the child's mother. There were no associated symptoms of pressure or pain. No personality changes, or heat or cold intolerance, or weight changes were noted.

*Past History:* The physical and mental development as judged from the age at which the child walked and talked were within normal limits. The child did well in school. Measles, mumps and chicken pox, without sequelae were the only childhood diseases. A tonsillectomy had been performed 1 year before the onset because of recurrent bouts of tonsillitis.

*Family History:* Hypertension was present in both paternal grandparents. There were no known endocrine disorders. The patient had 2 sisters, 13 years and 5 years of age, in good health.

*Physical Examination:* Blood pressure 115/85, pulse 96, temperature 100.2. The child was well developed and nourished, alert and cooperative. A firm, somewhat nodular mass was present in the neck attached to the trachea. There were no other physical findings of significance.

*Course in Hospital:* The clinical diagnosis was a nontoxic nodular goiter. Hb 77%. WBC 10,400 (polys. 79%, lys. 16. Monos 5). A subtotal thyroidectomy was performed. The postoperative course was uneventful. About 3 months after the operation, the child began to gain weight rapidly, her eyelids became edematous and the BMR was found to be -20%. Thyroid, ½ gr. daily was given with complete remission of symptoms. Eight months after the operation, x-rays of wrists, elbows and knees showed normally developed epiphyses. Cholesterol was 233 mg. per 100 cc. and BMR -8%. The child was admitted to the hospital for re-evaluation 1½ years later. She had been maintained on thyroid extract during that period, with normal growth and

mental development. Her laboratory work up showed a cholesterol of 204 mg., calcium 10.8 mg., phosphorus 5.3 mg., and alkaline phosphatase 8.0 units, BMR—17%.

**Pathology:** The specimen consisted of 2 portions of thyroid tissue weighing 22 gm. The cut section was pale, tan, homogeneous and meaty in consistency. On microscopic examination, the gland appeared to be uniformly involved, and diffusely infiltrated by lymphocytes. Numerous germinal centers were present, acini were small, round and contained little colloid. Acinar cells were low to high cuboidal showing a typical acidophilic degeneration. There was no increase in fibrous tissue. Figure 3.

**Summary.** A total of 1,595 thyroidectomies performed since 1940 has been reviewed and 24 cases of non-specific thyroiditis were selected for analysis.

Eight cases formed a closely knit clinical and pathological entity characterized clinically by painful, febrile, rapid enlargement of the thyroid with a high incidence of symptoms of tracheal pressure and pathologically by the finding of numerous tubercles and giant cells but no tubercle bacilli;

We wish to thank Drs. Henry W. Louria, Frank Teller and Lewis H. Berson for permission to use their cases.

presence of dense fibrous connective tissues and presence of polymorphonuclear leukocytes in clusters within the tubercles. This is the subacute, pseudotuberculous thyroiditis group.

Seven cases corresponded rather closely to the original Riedel's struma and were so classified. Painless, relatively rapid, extraordinary firm thyroid enlargement was the clinical aspect and a pronounced diffuse fibrosis and lymphocyte and plasma cell infiltration were the pathological findings.

Nine cases of struma lymphomatosa were reviewed and so classified on the basis of a slow, large, painless thyroid growth displaying on microscopic examination a diffuse infiltration by lymphocytes with numerous follicles containing germinal centers, acidophilic degeneration of acinar cells and little increase in fibrous tissue. The youngest case on record in a child of six was reported.

The similarities and differences between the various groups was discussed and the literature reviewed.

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# SOME ASPECTS OF HYPERTENSIVE DISEASE OF PREGNANCY TREATED BY SPLANCHNICECTOMY\*

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It is definitely established that the existence of arterial hypertension before or during a pregnancy constitutes a complication of dangerous potentialities to the pregnancy. Also, the onset of hypertension during pregnancy all too frequently results in persistent hypertension for the mother. Our interest has been in hypertensive disease in general, and particularly in the surgical treatment of this disease. But problems of pregnancy in varied aspects have frequently confronted us in our management of hypertensive females by splanchnicectomy. It thus appeared advisable to investigate the relationship of the operation of splanchnicectomy to hypertensive disease of pregnancy.

Since November 1933 more than 2000 hypertensive patients have been treated at the University Hospital with the surgical procedure of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic gangliectomy. Half of them were females. Thirty-seven per cent of these women were less than 40 years old at the time of operation and thus were in the child-bearing age; 28 of them became pregnant after operation, with and without our counsel. The results of 34 pregnancies in these 28 splanchnicetomized patients are reported here.

During the past 5 years splanchnicectomy was performed during the second trimester of pregnancy in 5 additional cases, each suffering from severe toxemia superimposed upon prepregnant hypertension. This is a new therapeutic approach to a serious and vexing specialized problem.

Many observers<sup>1,5,13,14</sup> have postulated that hypertension of pregnancy is merely an accentuation of a frank or latent hypertension which existed prior to pregnancy, and some believe that a toxemic pregnancy does not injure normal vascular and renal systems. There is no unity of opinion concerning this important matter. It also has been generally assumed that females whose hypertension originates during pregnancy do not differ clinically from females whose hypertension is in no way related to pregnancy. In order to uncover information which might help clarify the foregoing, 452 females who were operated upon during the years 1934 through 1942 inclusive, and who have thus been followed from 5 to 13 years, were divided into 2 groups depending upon whether or not their hypertension was first discovered during a pregnancy. The 2 groups have been compared as to the extent of their hypertensive disease and as to the end-results from splanchnicectomy.

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*Pregnancy Subsequent to Splachnicectomy.* The hypertensive female who becomes pregnant is not likely to go through childbearing successfully. In the first place, she is markedly vulnerable to a toxemic pregnancy. Dexter and Weiss<sup>2</sup> followed 39 prepregnant hypertensives through pregnancy, and toxemia occurred in half of them.

Secondly, a toxemic pregnancy may permanently harm the mother. In the Dexter and Weiss series, approximately one quarter of those who developed toxemia manifested higher blood pressure levels and more extensive hypertensive disease after the pathological pregnancy than before. Reid and Teel<sup>13</sup> followed 122 patients with known essential hypertension prior to pregnancy, and at a late postpartum examination, 44% of them showed higher blood pressure levels than when first seen.

Thirdly, the fetal prognosis is discouraging for prepregnant hypertensives. Hypertension in the mother definitely interferes with the well-being of the fetus. Dieckmann and Brown<sup>1</sup> found a 21% fetal mortality in mothers who had essential hypertension. For the 122 patients in the series of Reid and Teel<sup>13</sup> the fetal mortality was 21.9%. It is thus seen that pregnancy in an already hypertensive female is likely to have a disappointing, and sometimes tragic, ending.

We have followed 28 hypertensive females who were first treated by splachnicectomy and who subsequently experienced pregnancies; the data for each case are given in Table 1. Naturally, they were relatively young at the time of the operation, their average age being 28 years. The average duration of hypertension from the time of its discovery until operation was 4.2 years. The average preoperative blood pressure was 208 systolic, and 135 diastolic.

Angiospastic retinitis was present prior to operation in 21 of the 28. Two

cases had severe neuroretinitis with papilledema.

When these 28 patients were classified according to our preoperative clinical classification of arterial hypertension,<sup>10</sup> 10 cases were in group three, in which organic heart disease is predominant, the diagnosis being confirmed by either a definitely abnormal electrocardiogram or a teleoroentgenogram showing cardiac enlargement or both. Five patients were in group five, cases in which impaired renal function is predominant. It is thus seen that hypertensive disease was already well-established in these 28 females before splachnicectomy.

The average time interval between operation and the subsequent pregnancy was 2.6 years, and the average blood pressure level prior to pregnancy was 144 systolic and 94 diastolic, for all 28 cases.

**Results.** Eighteen cases began pregnancy with normal blood pressures as a result of splachnicectomy. Seventeen of these females gave birth to 18 normal, living infants.

But on the other hand, of 10 women who started pregnancies with blood pressure levels above normal (greater than 150/90), only 2 delivered living infants at term. Case 10 began pregnancy with a blood pressure of 152/108, and Case 24 entered pregnancy with a blood pressure of 210/130; in each instance the hypertensive state was uninfluenced by the pregnancy. The remaining 8 women who began pregnancy with elevated blood pressure levels no matter how slight, either had to be interrupted or gave birth to still-born fetuses.

No patient whose blood pressure was within normal range prior to pregnancy developed a toxemia of pregnancy. Without such a good result from splachnicectomy, the expected incidence of toxemia would have been

50%; and the 10 splanchnicectomized females who began 14 pregnancies with elevated blood pressure levels did show exactly a 50% incidence of toxemia.

Twelve cases maintained blood pressure levels entirely within normal limits throughout 13 full-term pregnancies; one case maintained normal blood pressure throughout 2 pregnancies subsequent to splanchnicectomy. Mild to moderate elevations of blood pressure occurred in 14 pregnancies, in 5 of which living infants were delivered at term. In only 4 cases did the blood pressure during pregnancy reach or exceed the pre-splanchnicectomy level; each was interrupted.

Each of these 28 females who had pregnancies subsequent to splanchnicectomy have been examined recently. The time interval between the examination and the previous delivery averaged 2.7 years. Blood pressure levels were being maintained within normal limits (150/90 or less) in 15 cases, or 53.6%. Prior to splanchnicectomy the blood pressure levels of these 15 patients averaged 200/126.

In 9 patients the recent examination revealed mildly elevated blood pressure levels in the range of 150 to 170 systolic, and 105 diastolic. Prior to operation the average blood pressure in these 9 cases was 233/137. Only 4 cases recently showed blood pressure levels greater than 170/105.

It is readily apparent that it is inadvisable for the hypertensive female who does not obtain a good result from splanchnicectomy to hazard a pregnancy, for her chances of obtaining a living infant are meager. On the other hand, the once hypertensive female who maintains a normal blood pressure following splanchnicectomy, can be assured that if she does become pregnant, her chances are excellent for delivery of a living infant, and that she has probably been protected against any related vascular damage. In this

group of splanchnicectomized females, pregnancy following operation resulted in no harmful hypertensive complications.

The experiences of Newell and Smithwick<sup>7</sup> confirm the foregoing. They have reported the results in 14 hypertensive females who were treated by lumbodorsal splanchnicectomy and who then had a subsequent pregnancy, except for 1 case in which operation was performed during the first trimester. Thirteen infants were living and well. Only 1 pregnancy had to be interrupted. Six weeks postpartum, the average blood pressure of the series was 133/87.

*Splanchnicectomy Performed During Pregnancy.* A toxemia superimposed upon prepregnant hypertension presents a discouraging problem. Almost always the only recourse is interruption of the pregnancy. A new approach to this specialized problem has been tried at the University Hospital during the past 5 years. The operation of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy has been performed during the second trimester in 5 such cases which have been reported in detail<sup>12</sup>.

This surgical treatment is aimed directly at the underlying hypertensive disease, for it is felt that the complicating toxemia is a consequence of the pre-existing hypertensive state.

In 2 cases, the results have been excellent; following operation in both, the toxemia disappeared, normal blood pressure levels were achieved, living infants were obtained, and normal blood pressures have persisted for 4 years and 2 years respectively since delivery.

In the remaining 3 cases the operation exerted no influence on the toxemia, but in 1 of the cases the blood pressure levels since delivery have been significantly decreased as compared to the prepregnant levels.

*Hypertension Having Its Onset During Pregnancy Differentiated from Hypertension With Onset Without Relation to Pregnancy.* The 452 hypertensive females who were operated upon during the years 1934 through 1942 inclusive have been divided into 2 groups depending upon whether or not their hypertension was first recognized during pregnancy. In 100 of them, elevated blood pressure was first noted at the time of a pregnancy; it is indeed likely that some of these cases may have had unrecognized high blood pressure prior to pregnancy, but since there is no way of determining this, it is impossible to correct for this unknown factor. In the remaining 352 females in this series, onset of hypertension had no relation to pregnancy.

The clinical picture of the hypertensive state of one group differs in

certain respects from that of the other, but it cannot be stated that the degree of hypertensive involvement in one group is greater or more serious than that of the other. Diastolic blood pressure levels prior to operation were higher in the group related to pregnancy; also organic heart disease was predominant in a greater percentage of the cases in this group than in the other. But the incidence of cerebrovascular accidents and malignant hypertension prior to operation was greater in the group whose disease did not have its onset in pregnancy. There was no significant difference as to age at time of operation or as to known duration of hypertension prior to operation.

Even though there was no remarkable clinical difference in the hypertensive state of the 2 groups, yet they

TABLE 2.—SURVIVAL TABLE AFTER SPLANCHNICECTOMY FOR 89 FEMALES WHOSE HYPERTENSION BEGAN DURING PREGNANCY, EXCLUDING 11 CASES OF MALIGNANT HYPERTENSION

Years of Operation	Number of Cases	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 years
1934	1	100	100	100	100	100	100	100	100	100
1935	10	100	100	90.0	90.0	80.0	80.0	80.0	70.0	
1936	7	71.4	71.4	71.4	57.1	42.9	42.9	42.9		
1937	12	91.7	91.7	91.7	83.3	83.3	83.3			
1938	12	75.0	66.7	58.3	58.3	58.3				
1939	7	85.7	85.7	85.7	57.1					
1940	9	88.9	77.8	77.8						
1941	12	91.7	91.7							
1942	19	100.0								

TABLE 3.—SURVIVAL TABLE AFTER SPLANCHNICECTOMY FOR 291 FEMALES WHOSE HYPERTENSION HAD NO RELATION TO PREGNANCY, EXCLUDING CASES OF MALIGNANT HYPERTENSION

Years of Operation	Number of Cases	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 years
1934	8	87.5	62.5	62.5	62.5	62.5	50.0	37.5	37.5	37.5
1935	22	86.4	81.8	81.8	81.8	77.3	72.7	68.2	63.7	
1936	21	81.0	81.0	71.4	66.7	62.0	62.0	57.3		
1937	30	83.3	83.3	83.3	76.7	70.0	70.0			
1938	35	82.9	82.9	82.9	80.0	80.0				
1939	30	90.0	90.0	90.0	90.0					
1940	29	96.6	96.6	96.6						
1941	44	88.6	81.8							
1942	72	81.9								



significantly differ in their overall response to splachnicectomy. Both groups responded well to the operation, but the end-results are definitely better for the females whose hypertensive disease had its origin during a pregnancy. The postpartum-persistent-hypertensives show better survival rates and maintain lower blood pressure levels after splachnicectomy.

The survival tables (Tables 2 and 3) for both groups are remarkably good, and it is surprising that the survival rate among the females whose hypertension is related to pregnancy should be even better than that of the other females. In the former group of 89 hypertensive women (excluding 11 cases of malignant hypertension), 90% survived 5 years after operation; for

cases of essential hypertension in the computing of the foregoing survival statistics since the malignant type evidently represents a separable, fulminating phase of the disease. Our diagnostic criteria<sup>11</sup> for malignant hypertension are: (1) a rapidly-progressive, deteriorating, clinical course of recent onset; (2) severe neuroretinitis with definite papilledema of 1 diopter or more; (3) high diastolic blood pressure; and (4) evidences of constitutional involvement.

The group of females whose hypertensive state was related to pregnancy has maintained a better blood pressure response to splachnicectomy than the other group of female hypertensives, even though the response of the latter also has been good. Among the former

TABLE 4.—BLOOD PRESSURE RESPONSE IN 452 FEMALES, 5 TO 13 YEARS AFTER SPLACHNICECTOMY, INCLUDING CASES OF MALIGNANT HYPERTENSION

	Number of Cases	Now Normal	Marked Reduction (Of 80 mm. Systolic & 25 mm. Diastolic or More)	Significant Reduction (Of 40 mm. Systolic & 25 mm. Diastolic or More))	No Significant Change	Worse	Alive But No Recent B.P. Determination	Dead
Onset During Pregnancy	100	23 (23%)	22 (22%)	19 (19%)	4 (4%)	0	5 (5%)	27 (27%)
No Relation To Pregnancy	352	54 (15.4%)	48 (13.6%)	70 (20%)	32 (9%)	5 (1.5%)	35 (10%)	108 (30.5%)

the 29 cases operated upon 11 to 14 years ago, the 10-year survival rate was 76%. While for the second group of females with onset of hypertension bearing no relation to pregnancy, the 5-year survival rate was 86%, and the 10-year survival rate was 65.4%.

Post-splachnicectomy survival among malignant hypertensives whose elevated blood pressures were first discovered during pregnancy does not differ significantly from malignant hypertensives whose disease bears no relation to pregnancy. The cases of malignant hypertension have been dealt with separately from the other

group, 23% were maintaining normal blood pressure levels (150/90 and less) 5 to 13 years since operation, and in another 22% the blood pressure was markedly reduced by 80 mm. systolic and 25 mm. diastolic or more as compared to the preoperative level (Table 4). In the latter group, 15.4% were maintaining normal blood pressure levels, and another 13.6% showed marked reduction 5 years or more after operation.

*The Problem of Post-Toxemic Hypertension.* In large series of pregnancies, Stander<sup>15</sup> found an 8.4% incidence of toxemia, Dieckmann<sup>3</sup> a 6.7%, and

Page<sup>8</sup> a 9% incidence. Thus toxemia occurs in about 8% of all pregnancies.

Dieckmann and Brown<sup>5</sup> reviewed the literature and concluded that approximately one quarter of the patients with pre-eclampsia and eclampsia develop permanent hypertensive disease after pregnancy. Herrick and Tillman<sup>6</sup> also found that 25% of women who have had a toxemic pregnancy, are left with permanent postpartum vascular disease. Peckham<sup>9</sup> reported a much higher incidence (63.4%) of chronic vascular damage as the late result in 500 cases of toxemia of pregnancy. Reid and Teel<sup>13</sup> were very careful in determining that both the pre-pregnant blood pressure and urine were normal in a series of 235 patients who later developed mild pre-eclampsia; 21% had sustained hypertension 6 months to 3 years postpartum. Simrall<sup>14</sup> followed 91 patients who developed toxemia during pregnancy and who definitely had normal blood pressure levels prior to pregnancy or during the first trimester; at a late postpartum examination he found that 30% manifested abnormally elevated blood pressure.

Since roughly 25% of females who have had a toxemic pregnancy are left with permanent postpartum hypertension, and since toxemia occurs in about 8% of pregnancies, then about 2% of all women who become pregnant may be expected to develop permanent hypertension as a result of pregnancy.

There were 3,440,000 births in this country in 1946. The stillbirth rate was 27 per 1,000 live births. Of the 3,500,000 women who went through pregnancies in the single year of 1946, possibly 70,000 now have permanent hypertensive disease. The problem of post-toxemic hypertension is thus one of considerable magnitude; it is also serious enough to warrant thought and action by the physicians responsible for the welfare of these women.

These females who are now hypertensive as a result of pregnancy constitute a group in whom excellent results can be expected from splanchnicectomy. Five to 13 years after operation one quarter of this group can be expected to be maintaining normal blood pressure levels. The operative risk is minimal, providing the disease has not yet progressed to its malignant phase. The operative mortality for all females, excluding cases of malignant hypertension, is 0.5%. For females with malignant hypertension, the operative mortality is 7.7%.

At the present time the operation of splanchnicectomy represents an effective therapeutic approach to hypertensive disease, and it is especially efficacious in coping with the problem of post-toxemic hypertension. This operation must be considered for the female whose blood pressure persists at hypertensive levels for more than one year following childbirth.

**Summary and Conclusions.** 1. The large number of female hypertensives who were treated with bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy at the University of Michigan Hospital afforded an opportunity to study several aspects of hypertensive disease of pregnancy.

2. Twenty-eight hypertensive females who were treated by splanchnicectomy, subsequently experienced 34 pregnancies. Of 18 cases who began pregnancy with normal blood pressures, 17 gave birth to 18 infants, and 15 were still maintaining normal blood pressure levels at a recent examination, averaging 2.7 years since delivery and 6.3 years since operation. On the other hand, of 10 cases who started pregnancies with blood pressure levels above 150/90, only 2 delivered living infants at term.

3. Not one of 18 cases who responded to splanchnicectomy by maintaining

normal blood pressure levels after operation and who subsequently became pregnant developed a toxemia of pregnancy.

4. No splachnicectomized female suffered any late, harmful vascular effects as the result of pregnancy.

5. Five cases of toxemia superimposed upon prepregnant hypertension have been treated by splachnicectomy performed during the second trimester of pregnancy, and in 2 cases the results have been excellent. Following operation in both, the toxemias disappeared and normal blood pressure levels were achieved for the remainder of the pregnancies and during a long postpartum follow-up period.

6. When female hypertensives are divided into 2 groups depending upon

whether or not their hypertension had its origin during a pregnancy, there is little variance in their disease pictures, but there is significant difference in their overall response to splachnicectomy. Both groups respond well to the operation, but the end-results are definitely better for the females whose hypertensive state began in a pregnancy.

7. The young hypertensive female who wishes to have children should first have the essential hypertension treated by splachnicectomy. If she maintains normal blood pressure levels for 1 year after operation, she may with reasonable safety become pregnant and with the assurance that her chances are excellent for giving birth to a normal infant.

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# THE SECRETORY RESPONSE TO HISTAMINE IN INDIVIDUALS WITH A NORMAL AND ABNORMAL GASTRIC MUCOSA

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ALTHOUGH numerous studies have been made of the clinical and gastroscopic aspects of gastritis,<sup>2</sup> to our knowledge, a definitive correlation of the appearance of the gastric mucosa with its secretory capacity has not been made. The purpose of the present paper is to report such an analysis.

phy, as evidenced by grayness of the mucosa and visible capillaries ("atrophic gastritis"); (c) 50 with inflammatory changes in the mucosa, including edema, erythema and exudate ("chronic superficial gastritis"); and (d) 50 cases with an irregular cobblestone-like mucosa, ("chronic hypertrophic gas-

TABLE 1.—CORRELATION BETWEEN GASTROSCOPIC APPEARANCE OF THE MUCOSA AND HISTAMINE-STIMULATED SECRETION

Maximum Free Acidity (Clinical Units)	Normal Mucosa (100 pats.)	Atrophy <sup>o</sup> (50 pats.) per cent	Inflammatory <sup>oo</sup> Changes (50 pats.) per cent	Cobblestone-like Mucosa <sup>ooo</sup> (50 pats.) per cent.
Achlorhydria	5	30	30	2
1-20 units	1	10	6	2
21-40 units	5	2	18	10
41-60 units	18	16	14	12
61-80 units	20	16	6	26
81-100 units	22	10	14	22
More than 100	29	16	12	26
Total (per cent)	100	100	100	100

<sup>o</sup> "Atrophic gastritis"

<sup>oo</sup> Erythema, edema, exudate ("superficial gastritis")

<sup>ooo</sup> "Hypertrophic gastritis"

A study was made of 250 patients in whom the physical and laboratory examinations were normal and in whom complete roentgen studies of the gastro-intestinal tract were negative.

These cases were divided into 4 groups: (a) 100 with a gastroscopically normal mucosa; (b) 50 with atro-

tritis"). Gastric acidity was measured by the histamine test using 0.1 mg. of histamine hydrochloride per 10 kg. body weight; fractional specimens were obtained every 10 minutes for 1 hour; the values are expressed as clinical units of the maximum free acidity in any specimen.

**Results and Discussion.** The findings are listed in Table I.

Among the 50 patients with atrophy, there were 15 with histamine achlorhydria. The degree of atrophy in this subgroup is indicated in Table 2. It is of

TABLE 2.—TYPES OF ATROPHY IN HISTAMINE ACHLORHYDRIA

Type	No. Patients
Patchy atrophy	3
Generalized atrophy	12
Slight	0
Moderate	3
Severe	9
Total	15

interest that the maximum free acidity exceeded 40 clinical units and rose as high as 126 units in 29 of the 50 patients with atrophic changes. The type of atrophy in this subgroup is shown in Table 3. Except for this observation,

TABLE 3.—TYPES OF ATROPHY IN PATIENTS WITH ACIDITIES ABOVE 40 CLINICAL UNITS

Type	No. Patients
Patchy atrophy	8
Generalized atrophy	21
Slight	7
Moderate	10
Severe	4
Total	29

there was no significant correlation between the level of free acid and the gastroscopic appearance of the gastric mucosa in this series of patients.

It is apparent that atrophic, inflammatory, or hyperplastic changes of the mucosa do not necessarily alter the secretory response to histamine stimulation. This finding is in agreement with that of Schindler *et al.*,<sup>3</sup> who, in a study of 82 cases of spontaneous histamine achlorhydria, observed various types of gastritis as well as a normal mucosa. The present data, in accord with the observations of Schindler, demonstrate that the most common

anatomic basis for anacidity is diffuse inflammation and atrophy. The incidence of anacidity in patients with inflammatory and with atrophic changes was 30%, in contrast to 5 and 2%, respectively, for individuals with a normal mucosa and for patients with hyperplastic alterations.

Inflammatory changes with achlorhydria suggest involvement of the acid-secreting cells deep in the pits of the glands and not a mere "superficial gastritis". In a previous study of achlorhydria produced by roentgen irradiation,<sup>1</sup> it became evident histologically that the edema, erythema and exudate of the mucosa, as seen gastroscopically, were not limited to the superficial layers of the stomach but involved both the mucosa and submucosa. Such anatomical differences probably explain the variability of gastric secretion in patients with gastritis.

It is interesting that of the 50 patients with definite atrophy, 29 were able to secrete gastric juice with a free acidity above 40 clinical units. In 21 of these, the atrophy was diffuse and in 4 it appeared to be extremely severe. This finding indicates that numerous, well functioning, acid-secreting cells may be present, even though the atrophy as seen gastroscopically may seem to be pronounced.

**Conclusions.** 1. The correlation between the maximum free acidity and the gastroscopic appearance of the gastric mucosa is not exact.

2. Achlorhydria may occur with a normal mucosa, as well as with various types of gastroscopic alterations. However, in the present study, achlorhydria was observed in only 5% of individuals with a normal mucosa and in only 2% of those with a cobble-stone (hypertrophic) mucosa, as compared with an incidence of 30% each in patients with atrophy (atrophic gastritis) and with inflammatory changes (superficial gastritis).

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# THE GASTROSCOPIC APPEARANCE OF THE GASTRIC MUCOSA IN PEPTIC ULCER

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RECENT studies have demonstrated significant differences in the maximum free acidity of the gastric secretion between patients with gastric and those with duodenal ulcer. The maximum free acidity after histamine was low in 21% of the gastric ulcer group, whereas in duodenal ulcer it uniformly exceeded 50 clinical units.<sup>10</sup> The output of acid in the 12 hour night secretion averaged 273 mg. in gastric ulcer, 661 mg. in a series of normal individuals, and 2242 mg. in the duodenal ulcer.<sup>6</sup> A comparison of the maximum free acidity and the gastroscopic findings in individuals without demonstrable organic disease of the gastrointestinal tract indicated no exact relationship.<sup>9</sup> However, achlorhydria was noted in 30% both of patients with atrophic and of those with "superficial" inflammatory changes, in contrast to an incidence of 5% among individuals with a normal gastric mucosa and 2% among those with hypertrophic changes.

The present study was undertaken: a) to compare similarly the gastric acidity and the gastroscopic findings in patients with gastric ulcer and with duodenal ulcer, and, b) to seek a possible explanation for the pronounced difference in gastric secretion between the two ulcer groups.

*Present Study.* Two consecutive se-

ries of patients with duodenal and gastric ulcer were collected; individuals with gastroenterostomy, gastric resection, or vagotomy were not included. Gastric acidity was measured by the histamine test (0.1 mg. per 10 kg. body weight) and expressed in clinical units of the maximum free acidity as determined during the conventional one hour procedure.

The gastroscopic findings were classified as: a) normal, b) atrophy (so-called "atrophic gastritis"), c) an irregular cobblestone-like mucosa (so-called "hypertrophic gastritis"), and d) edema, hyperemia, and adherent exudate (so-called "superficial gastritis"). The presence of erosions and hemorrhagic areas was noted in groups b, c and d, but not considered in this study.

*Gastric Ulcer.* Among 150 consecutive cases of benign gastric ulcer the gastric mucosa distant from the ulcer appeared normal in 45% and abnormal in 55% (Table 1).

TABLE 1.—GASTROSCOPIC APPEARANCE OF THE GASTRIC MUCOSA IN GASTRIC ULCER (150 Cases)

Mucosa	No. Cases	Per cent
Normal	67	45
Edema, erythema, exudate	16	10
Hyperplastic features	28	19
Atrophy	39	26
Total	150	100

The correlation between the gastroscopic changes and the maximum free acidity is expressed in Table 2.

tion may occur with any type of gastric mucosa, the only essential being the presence of free hydrochloric acid.

TABLE 2.—CORRELATION BETWEEN APPEARANCE OF THE MUCOSA AND MAXIMUM FREE ACIDITY IN GASTRIC ULCER (120 Cases)

Maximum Free Acidity (Histamine) Clinical Units	Normal	Atrophy Per cent of Cases	Hyperplastic Features	Edema, Erythema, Exudate
1-20	7	30	4	26
21-40	8	10	10	12
41-60	16	20	21	12
61-80	16	26	20	19
81-100	32	10	22	12
More than 100	21	4	23	19
Total	100	100	100	100

*Duodenal Ulcer.* One hundred consecutive cases of duodenal ulcer had one or more gastroscopic examinations. The mucosa consistently appeared normal in 47% and abnormal in 53% (Table 3). In these 100 cases erosions were observed in 11 and a benign polyp in one patient.

TABLE 3.—GASTROSCOPIC APPEARANCE OF THE GASTRIC MUCOSA IN DUODENAL ULCER (100 Cases)

Mucosa	No. Cases
Normal	47
Edema, erythema, exudate	7
Hyperplastic features	41
Atrophy	5
Total	100

The gastroscopic findings and the maximum free acidity are correlated in Table 4.

**Discussion.** The present analysis again demonstrates that peptic ulcera-

Previous gastroscopic studies<sup>2,4,7,11,14</sup> in patients with duodenal ulcer have yielded varying figures both for the incidence and the type of gastritis. The present study, however, indicates a considerable difference between gastric and duodenal ulcer in the appearance of the gastric mucosa. Thus, a cobblestone-like mucosa was noted in 41% of patients with duodenal ulcer and in only 19% of cases with gastric ulcer. Perhaps of greater significance is the fact that atrophy was recorded in only 5% of cases with duodenal ulcer in contrast to 26% of those with gastric ulcer. Among 18 patients with gastric ulcer and a low free acidity, inflammatory changes (edema, erythema, exudate) or diffuse atrophy were observed in 13. Of particular interest in this regard are the observations of Meyers<sup>9</sup> who, in a recent study, noted that the

TABLE 4.—CORRELATION BETWEEN APPEARANCE OF THE MUCOSA AND MAXIMUM FREE ACIDITY IN DUODENAL ULCER

Maximum Free Acidity (Histamine) Clinical Units	Normal	Atrophy Per cent of total number of Cases	Hyperplastic Features	Edema, Erythema, Exudate
1-20	--	--	--	--
21-40	--	--	--	--
41-60	1	1	2	1
61-80	6	2	9	1
81-100	14	--	9	1
More than 100	26	2	21	4
Total	47	5	41	7



number of parietal cells per high power field in the gastric fundus of patients with gastric ulcer varied from 0 to 40, whereas in duodenal ulcer the cell counts ranged from 60 to 90. The incidence of atrophic changes in gastric ulcer has been reported previously as 13%,<sup>5</sup> 6%,<sup>13</sup> and zero<sup>7</sup>; Baker<sup>1</sup> records an incidence of 60%.

This difference in the appearance of the gastric mucosa between duodenal and gastric ulcer coincides in many cases with the pronounced difference in gastric secretion observed in these two groups.

Conclusions. 1. The gastric mucosa

in duodenal and in gastric ulcer gastroscopically may appear normal, atrophic, hyperplastic or present inflammatory changes—erythema, edema, and exudate.

2. The incidence of atrophy of the gastric mucosa is considerably higher in gastric than in duodenal ulcer, whereas the incidence of a hyperplastic mucosa is considerably higher in duodenal than in gastric ulcer.

3. The frequency of atrophic and inflammatory changes of the gastric mucosa in gastric ulcer accounts in the majority of the cases for the low output of acid.

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# DIABETES AND VASCULAR DISEASE IN YOUTH\*

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THE frequency of advanced arterio-sclerotic, renal and retinal lesions in youthful diabetics is becoming more fully appreciated. The total number of youthful diabetics in the United States is not accurately known, but the facts concerned with an estimate of the diabetic population available in 1946 were reviewed by Joslin *et al.*<sup>11</sup> Patients between the ages of 15 and 30 years include: (a) those whose diabetes began in childhood and have

Blotner and Hyde<sup>2</sup> studied 45,000 consecutive selectees from ages 18 to 45 years at the Armed Forces Induction Station. They found diabetes to be about 3 to 4 times that of the National Health Survey. These figures were confirmed in a study by the National Youth Administration.<sup>6</sup> Among 1,47,813 youths age 16 to 24 years, glycosuria was present in 2.6%. There were 178 known diabetics, or 1.2 per 1,000. More recent still is the survey conducted by

TABLE 1.—DIABETES IN YOUTH

Population Continental United States July 1, 1945		Massachusetts Selectees No. Diabetics per 1000 Registrants		National Health Survey No. Diabetics per 1000	
Age	Total	Age		Age	
All	139,621,431	All	4.6		
15-19	11,651,506	18-25	2.0	15-24	0.6
20-24	12,157,729	26-30	3.5		
25-29	11,469,639	31-35	6.2	25-34	0.9
30-34	11,006,658	36-40	6.1		
35-39	10,151,305	41-45	10.6	35-44	2.0
40-44	9,400,648				

survived many years of diabetes, (b) those with diabetes beginning between 15 and 30 years, recognized and unrecognized, (c) finally, those who will sooner or later develop diabetes. The National Health Survey by the National Institute of Health in 1935-1936 disclosed 9,182 diabetics in an urban population of 2,500,000.<sup>11</sup> This information was based upon a house to house campaign but without tests of the blood sugar. However, surveys have become available based on actual blood and urine chemical tests which give quite a different picture. Thus,

members of the United States Public Health Service in Oxford, Massachusetts, in which it was shown that for every 40 known diabetics there were 30 unknown cases. The estimated incidence for diabetes in this youthful period was 3 or 4 times that of the National Health Survey. In Table 1 are given the population at ages 15 to 45 estimated as of July 1, 1945, for the United States, and the frequency of diabetes in the youthful groups from an editorial in the Journal of the American Medical Association.<sup>1</sup>

An estimate of 36,523 cases of dia-

\* Aided by grants from the Eaton Laboratories Fund and the Life Insurance Medical Research Fund.

betes between 15 and 35 years, based upon the National Health Survey, seems too low. Yet an estimate of 84,000 for the ages 15 to 30 years, based on Massachusetts selectees, may be excessive. One may safely estimate that there are at present between the ages of 15 and 30 years 60,000 cases of diabetes. More important, however, are the indications of a continued increase in the next few years. Thus the United States population may reach a maximum by 1985 when it will be 22% greater than it was in 1940.\* At the same time the diabetic population may increase by 74%. One may safely add, therefore, to the total number of patients between the ages of 15 and 30 years who now have diabetes a minimum of 25%, or 15,000 who will develop it within the next few years.

The importance of vascular lesions in older diabetics has long been familiar to students of the disease. Now the excessive development of vascular nephritis, hypertension and retinitis in poorly controlled diabetics of long duration looms large on the horizon even in youth. Among 148 diabetics with onset of diabetes between 15 and 30 years of age, 64% show retinal hemorrhages and increased capillary fragility after 10 years of diabetes.<sup>10</sup> Although many influences, metabolic, infectious and endocrine may play important parts in the causation of these lesions at an early period, deficiency of one hormone, insulin, must be given primary consideration as the underlying factor. In youthful diabetics, the onset and course of vascular complications may be long observed. Additional necropsy data are needed, but are difficult to obtain owing to the improvement in treatment with consequent prolongation of life.

Between 1938 and 1946 clinical and post mortem records of the New

England Deaconess Hospital include 10 patients whose diabetes began before the age of 20 years and 2 others with onset at 22 and 27 years with diabetes of 0.2 to 20 years duration. Millard and Root<sup>9</sup> found that in 5 whose diabetes was of less than 5 years duration, no vascular complications were present. In 7 of these 12 patients, whose death occurred at ages between 25 and 32 years, coronary arteriosclerosis with partial or complete occlusion was present. Nephrosclerosis was present in 6 of the 7 and intercapillary glomerulosclerosis was present in 3. The globular masses of hyaline material between or within the glomerular capillary walls described by Kimmelstiel and Wilson, present in 3 cases, emphasize the fact that this lesion is as typical of diabetes in youth as in later life. A striking feature of the post mortem examinations of these 7 youthful cases with diabetes of more than 10 years duration is the fact that the arterial lesions are not of a single character. They involve all 3 of the common types: (1) calcification and sclerosis of the media of the Mönckeberg type; (2) intimal atheromatosis involving the aorta as well as the coronary arteries; and (3) arteriolar sclerosis evident especially in the kidneys, but also in splenic and pancreatic vessels. The lesions are identical with those seen in diabetes of later life. It must be concluded that it is the long duration of diabetes which in some way causes the lesions.

In the study of the pathology found at autopsy among 606 cases of diabetes, 290 males and 316 females, reported from the University of Minnesota by E. T. Bell,<sup>1</sup> 78% of the deaths were of persons over 50 years of age. Only 18 cases were under 20 years and 21 cases between 20 and 30 years of age. It does not appear from the discussion

\* These estimates are based upon the "medium" forecast of population published by Thompson and Whelpton in *Estimates of the Future Population of the United States, 1940-2000*, National Resources Planning Board, Washington, D. C., Table 7, page 68.

that any material was available on patients whose diabetes began in childhood and who had survived 12 or more years of diabetes. Twenty % of the cases died in diabetic coma. Gangrene and coronary disease together accounted for 27.2%. Pyelonephritis accounted for 1% (6 cases), and uremia for 0.7% (4 cases). By combining deaths from coma, infection and vascular disease, Bell concluded that 66.3% of diabetics die of complications related to the diabetes. It is not strange that in a series lacking youthful patients with diabetes of long duration it would be easy to conclude that intimal thickening in small renal arteries occurred after the age of 50 years easily. After 50 years of age it was five times as frequent in the diabetics and was more intense than in the control series of non-diabetic autopsies. Yet Bell's 15 cases, aged 10 to 20 years, showed in 20% slight arteriosclerosis and in 25% of 20 cases between 20 and 30 years of age arteriosclerosis of grades 1 and 2 was present. It is this renal arteriosclerosis which is a striking feature in the autopsies of our juvenile diabetic patients who have survived diabetes 12 to 15 years. Dr. Bell states that a thick homogeneous hyaline deposit in the arterioles is strong evidence of diabetes. It seems clear that in some way diabetes brings about at an early stage in life hyaline changes in the arteries and arterioles with consequent hypertension and renal disease. Possibly the hyaline masses in the glomeruli are so closely related to arteriosclerosis that they should be regarded as dependent upon the same fundamental etiology. Certainly the large nodular lesions are almost pathognomic of diabetes. In Bell's series of 40 diabetics from 1 to 30 years of age, neither nodular nor diffuse "intercapillary" lesions occurred, but they were frequent from 50 years onward. The

association of the "intercapillary glomerulosclerosis" with arteriosclerosis and arteriosclerosis of larger vessels is evident in Bell's series and in our patients.

In the series of Gauld, Stalker and Lyall,<sup>7</sup> 12 of the 24 diabetics reported developed progressive renal complications after diabetes of long duration. In 6 of the 7 cases observed post mortem, Kimmelstiehl-Wilson lesions and nephrosclerosis were present. They also comment upon the presence of pyelonephritis in 3 cases.

That one must consider in diabetes not only the arteries but also the veins and capillaries has been clearly shown in recent years. Thus Root and Rodriguez<sup>10</sup> have studied capillary fragility in diabetes. In 26 cases with retinitis and increased capillary fragility, 11 were from 21 to 39 years of age. It is quite evident in young diabetic patients that change in capillary fragility occurs within 5 to 12 years after the onset of diabetes and is frequently associated with beginning evidences of vascular disease. Usually such patients will within a few months or a year or two begin to show retinal hemorrhages, subsequent to vascular disease. The nature of the change occurring in capillary vessels is yet undetermined and the place of such substances as rutin and ascorbic acid in its treatment is being investigated. In recent years increasing attention has been given to small venules in the retina. Dilatation of these venules and some of the hemorrhagic manifestations in the eyes in retinitis proliferans seems clearly due to disturbance in the veins.

These facts may indicate different etiologic factors are at work and that diabetes of long duration exerts a specific influence permitting early vascular damage of varying types. Clinical examination of 192 diabetics,<sup>13</sup> in whom diabetes began before the age of 15 years and who have survived 20

or more years of diabetes, showed calcified vessels by Roentgen-ray examination, albuminuria, hypertension or retinal hemorrhages in 86%. However, in 14% of these patients no such lesions were found, which gives hope that better treatment may postpone these changes in the future.

Three basic questions may be stated upon which divergent views have been expressed: (1) Is arteriosclerosis a cause or an effect of diabetes? There are still some physicians of experience who believe that arteriosclerosis causes diabetes. Such cases must be rare. On-

set of diabetes declines in frequency from the age of 60 onward. No case in 2,500 childhood diabetics has shown hypertension or arteriosclerosis at onset of the diabetes or developed it until diabetes has existed for periods from 5 to 15 years. (2) Is arteriosclerosis a complication of diabetes or is it an integral manifestation of the basic disorder which causes diabetes? Dry and Hines<sup>3</sup> postulated an inherent weakness in the diabetic constitution which affects both the insulin-producing tissues and the vascular system with a common mechanism for the

TABLE 2.—CAUSE OF DEATH ACCORDING TO DURATION OF DIABETES  
531 DIABETICS WITH ONSET PRIOR TO 30 YEARS OF AGE

Duration Diabetes at Death Years	Number Deaths	Coma %	Nephritis %	Heart %	Tuberculosis %	Pneumonia Sepsis %	Misc. %
0- 4.9	166	56	4	5	8	12	13
5-14.9	223	28	13	8	12	15	22
15-20 plus	142	3	30	32	7	9	19
Total Deaths	531	150	82	67	59	67	106

TABLE 3.—COMA AS CAUSE OF DEATHS IN YOUTH RELATED TO AGE AT ONSET  
AND DURATION OF DIABETES

Duration Diabetes at Death Years	0-14 Years		Age at Onset 15-20 Years		21-30 Years Plus	
	Deaths	Coma %	Deaths	Coma %	Deaths	Coma %
0- 4.9	78	71	37	46	51	38
5-14.9	95	31	37	16	91	18
15-20 plus	48	4	18	5	76	1

TABLE 4.—NEPHRITIS AS CAUSE OF DEATH RELATED TO AGE AT ONSET  
AND DURATION OF DIABETES

Duration Diabetes at Death Years	0-14 Years		Age at Onset 15-20 Years		21-30 Years	
	Deaths	Nephritis %	Deaths	Nephritis %	Deaths	Nephritis %
0- 4.9	78	4	37	5	51	2
5-14.9	95	11	37	11	91	17
15-20 plus	48	48	18	22	76	23
Total	221		92		218	

TABLE 5.—CALCIFIED ARTERIES IN 82 YOUNG DIABETICS RELATED  
TO DURATION OF DIABETES

Duration Diabetes Years	Average Age	Number Cases	Arteries Calcified %	Calcification Present		
				Aorta %	Pelvic Arteries %	Leg Arteries %
0-10	23.2	8	0	0	0	0
10-15	25.8	17	33.3	5.8	11.7	29.4
15-20	27.6	33	54.5	24.2	33.3	45.4
20-29	33.5	24	83.3	25.0	45.8	70.8

production of arteriosclerosis, retinopathy and neuropathy on the basis of involvement of the nutrient vessels to these structures. I disagree with this view. First, it would necessitate arteriosclerotic disaster for all diabetics, which in fact does not happen. Second, in time one should certainly find in some of the 2,500 children and another 2,000 with onset diabetes from 15 to 30 years of age, cases in which vascular disease preceded the diabetes. This has not been observed. (3 Are the arteriosclerotic complications of diabetes the result of changes characteristic of clinical diabetes? I believe the excessive arteriosclerosis in young diabetics of long duration is the result of uncontrolled diabetes and consequent features such as the poor resistance to infection with resultant pyelonephritis, pyorrhea, etc. In support of this view are cited 16 cases recently studied who now after 20 to 25 years of diabetes show no evidences of nephritis, arteriosclerosis by Roentgen-ray examination, or retinal hemorrhages.

*Causes of Death in Diabetes with Early Onset.* In Table 2 are shown the causes of death for 531 patients whose diabetes had its onset between infancy and 30 years of age. The series comprises 221 patients with onset of diabetes before their fifteenth birthday, 92 patients with onset between 15 and 20 years, and 218 patients with onset between 21 and 30 years. Coma caused 56% of 166 deaths occurring during the first 5 years of diabetes but thereafter it declined as a cause of death. In the group of 142 deaths occurring after 15 years of diabetes, it caused only 3%. The striking feature of this table is the increase in deaths from nephritis and arteriosclerotic heart disease to 30 and 32% of all deaths occurring after 15 years of diabetes. In Table 3 the place of coma in childhood is more clearly shown, since 71% of deaths occurring within 5 years after onset before the

age of 15 years were due to coma. Its virtual disappearance as a cause of death after diabetes had been present 15 years applied not only to the childhood but also to the cases with onset of diabetes between 15 and 30 years of age. An analysis of nephritis as a cause of death is given in Table 4. It is evident that among deaths occurring within 5 years duration of diabetes nephritis plays little part, from 2 to 5%, or actually only 6 deaths among 166 total deaths. After 15 years of diabetes, 48% of 48 deaths in patients whose diabetes began in childhood and 22% of 94 deaths in the other groups present the crux of the problem in the treatment of youthful diabetics, for it is the association of the renal lesions with hypertension, retinitis and later coronary disease, which most concerns us.

The relation of duration of diabetes to onset and development of vascular and renal lesions may be studied in various ways. In Table 5 are summarized the results of Roentgen-ray examinations of pelvic arteries, leg arteries and of the aorta (lateral films) in young diabetics. No calcification was found in cases with average age 28.2 years and with diabetes less than 10 years in duration. Thereafter, as the duration of diabetes increased, the incidence of visible calcification rapidly increased until 83.3% of cases with diabetes of over 20 years' duration showed calcified arteries. The arteries of the leg usually, but not always, show calcification first. Granted that calcification is a late stage in arteriosclerosis, it is still significant and especially in the pelvic arteries, where its grave prognostic import in pregnant diabetics of long duration has been emphasized by Priscilla White.

The high incidence of renal and vascular disease has been thought to be due to infections, endocrine factors, disturbed mineral metabolism, and uncon-

trolled diabetes. While it is true that diabetic patients are susceptible to streptococcus and staphylococcus infections, this group has not shown prior to the incidence of vascular disease or nephritis infections which could be related to them, except for pyelonephritis. Sharkey and Root<sup>12</sup> pointed out the excessive frequency of pyelonephritis in diabetics of long duration. Determinations of basal metabolisms, analyses of blood for such pituitary factors as follicle stimulating hormone and the excretion of 17 ketosteroids in a limited number of patients have not shown a clear picture. However, the studies of Selye<sup>11</sup> demonstrate experimentally the production of nephrosclerosis by means of injections of pituitary extract and the use of high protein-high salt diets. When the relation between the control of the diabetes as measured by hyperglycemia, glycosuria, acidosis and the faithful adherence to a prescribed diet are tabulated, there appears a striking correlation between lack of diabetic control and the development of vascular lesions. Thus, in 28 cases among the 192 diabetic children who survived 20 years of diabetes, Roentgen-ray examinations and clinical studies were normal, and in this group coma had only occurred in 17%. In 114 cases, calcified arteries in the legs or pelvic vessels were present with transient albuminuria, with hypertension and only one or two retinal hemorrhages. In this group, coma had been present one or more times in 38%.

Fifty patients were incapacitated with angina pectoris, progressive nephritis, cerebral accident, retinitis proliferans, and in them coma had been present in 74% one or more times. Coma represents maximal lack of diabetic control.

In considering the eye lesions of this group, one must abandon the idea that the retinitis follows, or is consequent

upon arteriosclerosis. The small round retinal hemorrhages, typical of diabetes, occur in patients without hypertension and before arteriosclerosis or albuminuria can be found. Frequently it is true these patients show increased capillary fragility and at present it appears probable these lesions are an essential and early stage of vascular disease. The striking thing about the retinal lesions of this young diabetic group is the tendency for progression from the stage of small hemorrhages to the stage of proliferation so commonly known as retinitis proliferans. In non-diabetics, on the other hand, small hemorrhages are frequently absorbed and only rarely stimulate proliferation of capillaries and fibrous tissue. This phenomenon is characteristic of a diabetic and seems in some way connected with the faulty metabolism of uncontrolled diabetes.

One must remember that, in the diabetic, disturbances of protein and fat metabolism, as well as of carbohydrate, do occur. To the ophthalmologist a faulty protein metabolism seems most likely to explain various phases of retinitis. The normal eye fluids contain no proteins only electrolytes, sugar and urea. Blood colloids are held back by the endothelium which is impermeable to colloids. There is an effective fluid exchange by osmosis. The abnormal ocular fluids contain protein and thereby break down the normal osmotic interchange. As a result the pressure within the eye increases. A breakdown of proteins in stagnant fluid gives toxic products promoting hemorrhage and the ingrowth of new capillaries. The abnormal kidney allows leakage of protein and edema.

Of 23 known amino acids, 10 are thought to be essential to life. The body can synthesize proteins from these amino acids in the liver. The body can form glycine but cannot form cystine, tyrosine or histidine.

Cystine is in a key position for the formation of amino acids into protein and it is a curious fact that in some diabetic patients there are hints of a disturbance in cystine metabolism. It is true that in diabetic animals made diabetic by alloxan a fall in the cystine of the blood occurs. Furthermore, administration of cystine impairs the effectiveness of alloxan in producing necrosis of the islands of Langerhans. This field is now being investigated with some promising preliminary results. One may say, therefore, that with respect to carbohydrate, fat and protein metabolism abnormalities occur in the uncontrolled diabetic, some of which may be directly related to the eye. Thus, the nitrogen balance in diabetic patients may be negative during periods of poor control and was often found negative during the early periods of treatment by under-nutrition. The evidences of liver disease affecting the formation of protein substances in diabetic patients is suggestive, although the large liver filled sometimes with glycogen, sometimes with fat, has not always been shown to be deficient in its protein-forming function.

The localization of the first evidences of arteriosclerosis is difficult. At present we try to carry out Roentgen-ray examinations of all diabetic patients in the juvenile group and of all other diabetic patients seen between the ages of 20 and 40 years. A summary of recent roentgenograms in 82 such cases is given in Table 5. We found that only 4 out of 24 patients with diabetes over 20 years failed to show visible calcification either in the arteries of the legs, pelvis or the aorta. In patients with diabetes from 10 to 20 years, calcification was absent in only 21 out of 50 patients. In 8 patients with diabetes less than 10 years, no calcification could be found. The average age when calcification was first seen varied from 26 years for the females with diabetes less

than 20 years to 31 years for the females with diabetes over 20 years. Apparently the duration of diabetes is the most important factor. As just stated, no calcification was found in patients with diabetes of less than 10 years' duration; in the 50 patients having diabetes from 10 to 20 years the average duration of diabetes was 15 years when the first evidence of calcification was seen; in the patients with diabetes for more than 20 years the average duration of diabetes was 20 years when calcification was noted. The last 2 groups show little difference in average insulin requirement. Thus, 44 units was the average dose for patients of long duration and 50 units was the average dose for the 50 cases of shorter duration. The average blood cholesterol value at the maximal was 306 for the females of less than 20 years' duration and 285 for the females of more than 20 years' duration. Males averaged 242 mg. and 296 mg. In this group of 74 patients, therefore, an increased plasma cholesterol has been an almost constant finding, not necessarily at the onset of the diabetes, but at some time during the course of the diabetes and frequently during the stage when albuminuria, hypertension, hypoproteinemia had developed. In a series of 26 young diabetics reported by Mann, Gardner and Root,<sup>8</sup> the plasma cholesterol values remained normal during the first years of diabetes, but became abnormally elevated on the average of 12 years after onset, when the first clinical evidence of renal disease became evident. In 36 patients the serum protein was over 6%, whereas in 18 cases the serum protein was under 6%.

**Summary.** The cause of death in patients whose diabetes begins in childhood and prior to the thirtieth year of age changes rapidly if death occurs after prolonged periods of the disease. Thus, acidosis and coma account for a majority of deaths which occur in the



first few years of diabetes, but it is only the cause of 3% of deaths in diabetic patients of this youthful group who survive more than 15 years of the disease. On the other hand, death from arteriosclerotic disease increased rapidly among those patients who have lived more than 15 years with diabetes. In patients with onset before 15 years of age, arteriosclerotic nephritis is a cause of 48% of the deaths which occur after 15 years of diabetes. In those patients whose diabetes begins between the fifteenth and thirtieth years, nephritis is similarly a major cause of death; but after 15 years of diabetes coronary disease becomes of equal prominence in this older group. The vascular disease of these young people is characterized by the fact that it affects all types of arteries. Atheromatosis of the larger vessels, arteriolosclerosis and medial calcification are found in various degrees. The renal lesions also are usually mixed, including the typical lesions of Kimmelstiehl disease and also typical lesions of pyelonephritis and chronic glomerulonephritis. Endocrine factors, infections, but chiefly loss of control of the diabetes itself are the prominent etiologic factors. In diabetic children the greater the frequency of diabetic coma, the more advanced the degree of vascular lesions found after a period of 15 years. Nevertheless, arteriosclerosis is not inevitable. Many cases after 20 years of diabetes fail to show retinal lesions or vascular disease. When the extraordinary improvement in the treatment of diabetes which has followed the introduction of insulin is considered, one cannot help but be

optimistic for the future and refuse to "sell American medicine short."

**Conclusions.** Vascular disease in diabetic patients in youth involves not merely the arteries and arterioles but also the veins and capillaries. Increased capillary fragility and retinal hemorrhages often are early findings. Changes in the retinal veins are common. Renal complications associated with vascular disease include the Kimmelstiehl-Wilson syndrome, hypertension, edema and albuminuria with hyalinization of arterioles. Chronic pyelonephritis is frequently the cause of renal failure, occasionally in association with arteriolosclerosis and nephrosclerosis, and occasionally glomerulonephritis. The striking fact that all types of arterial disease occur in these young diabetic patients after years of diabetes may suggest multiple etiologic factors—infections, endocrine and metabolic. However, the development early in life, the definite relationship between degree of diabetic control and the severity of these vascular lesions speak for an intracellular vulnerability to various etiologic factors conditioned by diabetes itself.

An estimate of 75,000 patients who now have diabetes or will soon develop it between the ages of 15 and 30 years in the United States is conservative. The need for a concerted study of the relations between the character of diabetic control, the proper use of insulin, the management of infections and the development of vascular disease in the kidneys, retina and heart stands as a challenge to pathologists and internists alike.

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# STUDIES IN HEPATIC GLYCOGEN STORAGE: I. ADRENALIN-INDUCED HYPERGLYCEMIA AS AN INDEX OF LIVER FUNCTION \* †

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THE production of hyperglycemia and glycosuria following the injection of adrenalin, was demonstrated by Metzgar,<sup>13</sup> Paton,<sup>11</sup> and Blum<sup>4</sup> shortly after the turn of the present century. It was subsequently demonstrated that such adrenalin-induced hyperglycemia failed to occur following hepatectomy in experimental animals and following ligation of the hepatic artery.<sup>8,12,15,17</sup> Loeper and Verpy<sup>11</sup> first evaluated blood sugar response in humans with liver damage, as contrasted to normal controls, and thought that the procedure could properly be utilized as a test of liver function. Brill in 1929,<sup>5</sup> Sucksdorff in 1930,<sup>16</sup> Althausen and his co-workers,<sup>1,2,6</sup> Loeb, Reeves, and Glasier in 1931,<sup>10</sup> and Cantarow and Ricchiuti in 1934<sup>7</sup> re-evaluated the procedure as a clinical test of liver function; but concluded that the adrenalin response was too unpredictable to permit its use as a quantitative instrument.

In all of the investigations above

mentioned, adrenalin was administered in dosage varying from 0.3 to 1.0 cc. of 1:1000 solution by hypodermic injection, to individuals whose dietary intake had been subject to no standardization in the days preceding the test. Bierry and Rathery<sup>3</sup> showed that adrenalin hyperglycemia may be significantly modified by diet. It seems probable that the inconstant results obtained by previous workers are referable to lack of adequate preliminary standardization (see later).

We first became interested in the procedure from a non-hepatic aspect; that is, from the standpoint of variation of hepatic glycogen storage in certain endocrinopathies. The investigation was pursued initially in a somewhat sporadic fashion, being chiefly concerned with the obtaining of control data in medical students and house officers, with an occasional observation on patients with endocrinopathies and hepatopathies. This portion of the work was

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finished in 1944, and will be noted below as Phase 1.

Phase 2 began in the Philippines in 1945. One of us, L.K., observed hundreds of patients suffering and convalescing from acute epidemic hepatitis. The majority of these patients on a regime of rest and adequate diet became clinically well within 4 weeks of the onset of jaundice. Those of us responsible for the management of these men had 3 major problems:

1. To determine, as early in the disease as possible, which men would convalesce in average time with a simple rest-diet regime, and which would develop the more serious degrees of hepatitis, requiring more strenuous therapy and prolonged hospitalization.

2. The evaluation of the effectiveness of therapeutic measures such as plasma, blood, and protein hydrolysate infusions.

3. The matter of determining when a post-hepatitis patient was ready to return to duty.

Considerable data were obtained during this period. Because of the lack of optimal control in some phases of the study, a report was delayed until such time as the work could be repeated on a smaller group under adequately controlled conditions.

Phase 3, begun in 1946, constitutes such a controlled study. The observations made in the tropics, under poorly controlled conditions, have been confirmed (see below).

**Results. Phase 1:** Only data on normal controls obtained during this period will be considered at this time. Liver glycogen storage in endocrinopathies and in response to hormone administration will be reported in a separate publication. Fifty-four observations were obtained on 39 adult males during this period. A dose of 0.01 cc. of 1:1000 solution of adrenalin (10 micrograms) per kg. of body weight

was arbitrarily selected as the standard amount to be administered intramuscularly. This dose has been used throughout this study except in a few individuals, in whom 4 sets of values were obtained—2 with the dose noted above, and 2 with larger dosage. No significantly greater blood sugar response was obtained in any instance with the larger dose.

By way of preparation, all control subjects received a high carbohydrate intake for 3 days prior to the test. The importance of this in other "carbohydrate" tests has previously been stressed.<sup>9</sup> Initially, the procedure was: 1. Fasting blood specimen for sugar determination; 2. Administration intramuscularly of 0.01 cc. 1:1000 adrenalin per kg. body weight; 3. Blood specimens at 15, 30, 45, 60, 90, 120, 180 minutes for sugar determination.

The curves so obtained, with rare exceptions, were essentially identical with those obtained in a normal glucose tolerance test. A composite presentation of the above data is shown in Figure 1.

In all but 1 instance in the first 20 controls, the maximal rise was obtained between the 30 and 60 minute periods. Since the purpose of the test was to measure maximal adrenalin response (maximal hepatic glycogenolysis), the procedure was simplified by obtaining only 0, 30, 45, and 60 minute blood samples and reporting the test in terms of difference between the fasting and maximal post-adrenalin blood sugars. This shorter procedure was followed in all subsequent tests.

These data show that blood sugar elevation in response to adrenalin administration under standard conditions in normal individuals ranges from 40 to 100 + mg. per 100 cc., with an average value of 58. This maximal elevation is obtained within 60 minutes following adrenalin administration.

*Phase 2.* 143 tests of hepatic glycogen

storage were performed on military personnel, all suffering or convalescing from acute epidemic hepatitis. Of these, 110 performed on 76 patients were reasonably well controlled from the standpoint of a diet adequate in calories and high in carbohydrate (by mouth or intravenously) for one or more days prior to the tests. The remainder could not

For descriptive purposes, the patients have been divided into 3 groups on the basis of intensity of the jaundice, and duration of the disease. Group 1 includes individuals with a maximal icterus index of 30 units and a duration of clinical jaundice of not more than 2 weeks. Group 2, those with a maximal icterus of 60 and maximal duration of

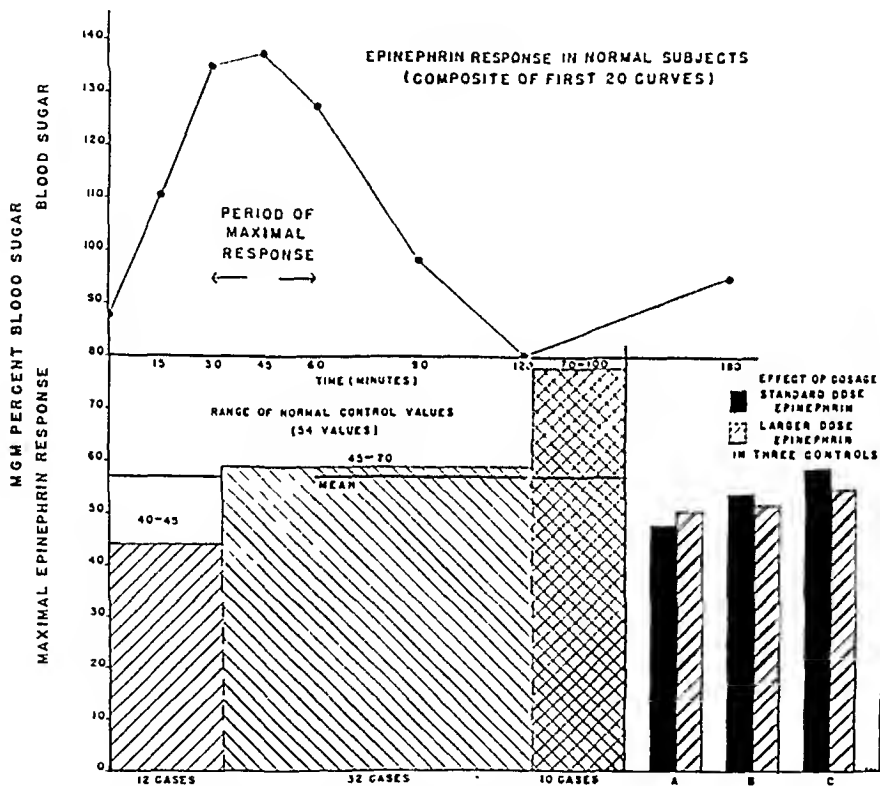


FIGURE 1.—Hepatic glycogen storage test—Adrenalin response in normal subjects, showing average curve, range, mean, and effect of dosage. The larger dosage does not significantly increase the maximal response.

be controlled adequately and are not included in these data. Long standing malnutrition in some of those patients included in the controlled group may very possibly have affected the adrenalin response, irrespective of the actual hepatic status of the individual. This was the major factor which led us to await Phase 3 before reporting our findings.

jaundice of 4 weeks. Group 3 includes all those with the most severe form of the disease. The findings are shown in Fig. 2. In more than 80% the glycogen storage test values included in these averages were obtained during the first 2 weeks of clinical jaundice. The correlation of the adrenalin response with the clinical course of the disease, and with the icterus index seems obvious.

Correlation with other liver function tests, and serial values in the same individual will be considered under Phase 3.

As stated before, 3 major questions needed to be answered in these men:—

(a) *Early Determination of the Probable Severity of the Disease.* It will be noted that the average response to adrenalin in the first and second weeks of the disease in Group 1 was within the normal range, and that glycogen storage test values in Group 2 more closely approached the normal than did those in Group 3. (b) *Evaluation of the Effectiveness of Therapeutic Agents.* Aside from diet, the only therapeutic agents used in this phase of the program were plasma, and pro-

Technic. The 3 day high carbohydrate, iso-caloric or hyper-caloric intake previously noted has been continued. In addition, between 8 and 10 p.m. the night preceding the test, the individuals under study received 8 ounces of fruit juice fortified with 2 ounces of glucose, the obvious purpose of all these measures being to obtain maximal storage of glycogen in the liver.

**Clinical Material.** Over a period of almost 2 years, a large group of patients with acute hepatitis in all phases and of all degrees of severity has been studied. The same statement applies to men with cirrhosis, *i.e.*, chronic, advanced liver damage, usually alcoholic in origin.

A small group of patients with chronic, non-resolving, viral hepatitis has also been the subject of intensive study.

All these men have been under unusually well controlled conditions with regard to food intake, activity, and clinical and chemical evaluation. A number have been on balance

CLASSIFICATION	NUMBER OF PATIENTS	MAXIMAL DURATION OF JAUNDICE	MAXIMAL ICTERUS INDEX	MAXIMAL EPIEPHRIN RESPONSE
MILD HEPATITIS	20	2 WEEKS	3.0	4.6
MODERATE HEPATITIS	34	4 WEEKS	6.0	3.2
SEVERE HEPATITIS	22	LONGER	20.0+	1.8

FIGURE 2—Adrenalin response of patients studied in Phase 2, with mild, moderate, and severe hepatitis. There was little overlapping between the 3 groups.

tein hydrolysates. To our considerable surprise, hydrolysates seemed to cause a more prompt clinical and chemical improvement than did plasma. This will be discussed further in another report. (c) *Determination of Complete "Cure" of the Hepatitis.* The glycogen storage test was not found to be a reliable index of "cure" in the sense of complete readiness for full activity. The adrenalin response usually became normal in the presence of an abnormal cephalin flocculation.

**Phase 3.** With the inauguration of the present University of California-Navy research program in the pathologic physiology of the liver, the further evaluation of this test under precisely controlled conditions was given high priority.

study regimes; that is, have had absolute constancy of dietary intake during most of their period of study.

**Findings. Acute Hepatitis.** In Fig. 3 are shown serial studies of 10 patients selected essentially at random from several score of such individuals. All 10 men were less than 30 years of age and had "classical" forms of the disease; all were severely jaundiced when first studied; all but one had histological confirmation of the diagnosis by one or more biopsies; and all eventually made complete chemical and clinical recoveries. Total bilirubin values are not shown in some instances because of the use instead, of the icterus index.

**PATIENT BAB—**Clinically this man made a moderately slow, but otherwise uneventful

recovery, and returned to his work as a butcher approximately 5 months after the clinical onset of the disease. He was readmitted to the hospital 3½ months later with a recurrence (or reinfection), from which he has

apparently completely recovered. The meaning of the variability of his glycogen storage test response during convalescence from the recurrence is not apparent to us at this time. PATIENT BRO—had an initially intense, but

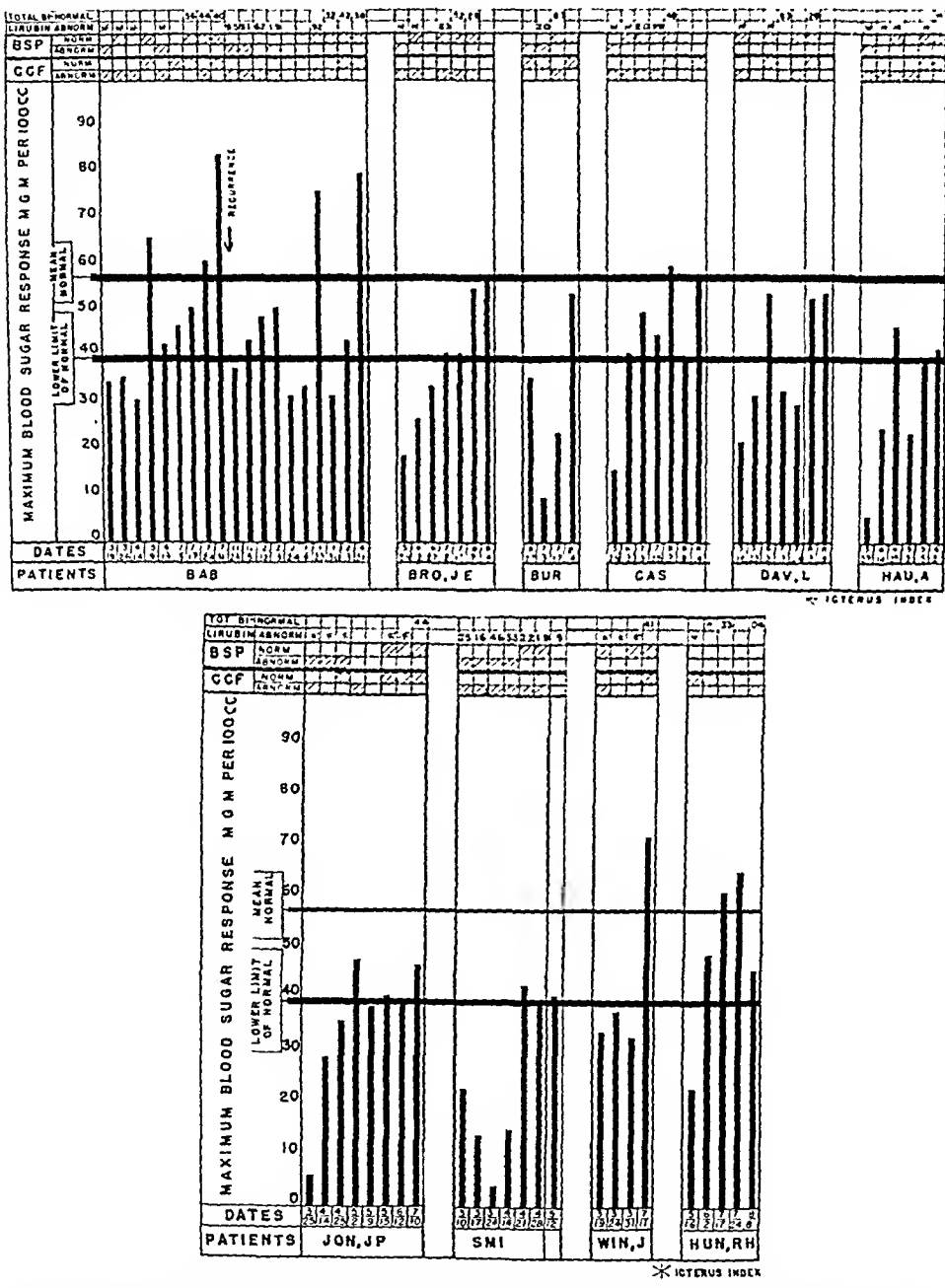


FIGURE 3—Serial hepatic glycogen storage values in 10 patients with acute liver damage (hepatitis), including correlation with 3 standard tests of liver function.

rapidly resolving hepatitis, the course of which is well indicated by the glycogen storage test.

PATIENT BUR—shows a glycogen storage test pattern which has been observed in many of these men—a normal or nearly normal value in the first day or two of the disease, followed by a drop to very low levels, and then a gradual rise, sometimes to high normal levels, the latter indicating, perhaps, major hepatocellular regeneration.

PATIENTS CAS, DAV, HAU, JON, SMI, WIN, and HUN—show varying degrees of the above findings.

As in the case of all tests of liver function with which we are familiar, there is no really close correlation of the glycogen storage test with any other laboratory procedure. In Fig. 4

standing cirrhosis. The acute flare-up was induced by a combination of an alcoholic debauch and congestive heart failure. His liver was loaded with fat. On adequate dietary and cardiac management, he made a rapid response, which is reflected in his glycogen storage test as well as in the other tests of liver function.

PATIENT DAN—This man had a typical, severe, alcoholic cirrhosis of approximately 20 years duration. During the entire period covered by the data presented (excepting only the last 2 values), he was under well controlled conditions on the hospital ward. During this time he made slow but steady clinical improvement. The last 2 values were obtained several months after the patient had left the hospital and was on a program of essentially full activity. The final glycogen storage test value was obtained after an all night bus ride

LIVER FUNCTION TEST	CORRELATION	NO CORRELATIONS	NUMBER OF OBSERVATIONS
CEPHALIN CHOLESTEROL FLOCCULATION	63%	37%	140
BROMSULFALEIN RETENTION	61%	39%	132
THYMOL TURBIDITY	60%	40%	78
ICTERUS INDEX	66%	34%	101

FIGURE 4—Correlation of glycogen storage test with 4 other liver function tests in a random group of patients with acute and chronic liver damage.

are findings in patients with acute and chronic liver damage, selected at random, indicating a correlation of this determination with 4 other simple tests of liver function considerably more than would be obtained by chance, and showing a surprising closeness of per cent correlation in all 4 tests.

*Chronic Liver Damage (Cirrhosis).* In Figure 5 are shown serial studies in 10 patients with cirrhosis of varying extent and acuteness. The findings in these men are capable of more exact interpretation than are those in the patients with hepatitis, because of the more slowly changing nature of the disease in the majority of instances. As in the hepatitis patients, the diagnosis has been proven in each individual by one or more biopsies.

PATIENT BEA—This 35 year old man was admitted in a hyperacute phase of a long

without adequate preparation in terms of preliminary high carbohydrate intake. Inasmuch as he was clinically vastly improved at this time, it can be assumed that this final value emphasizes the need for adequate preliminary preparation for the test.

PATIENT DRE—was one of the few patients in our group with irreversible, progressive liver damage. He died a few weeks after the last test shown.

PATIENT GRA—Very similar to patient BEA—an acute, severe flare-up of a long standing cirrhotic process. He eventually was discharged free of symptoms, although with considerable permanent damage to the liver.

PATIENT HAN—An aged male with pronounced intrahepatic portal hypertension and, to date, intractable ascites. We cannot explain the one normal bromsulfalein value.

PATIENT HAW—A young, alcoholic male, with a large liver showing surprisingly little fibrosis. Perhaps his extremely high glycogen storage test response may be explained on the basis of a liver in a hyperregenerative phase. Similar findings have been observed in one other comparable patient.

PATIENT NIB—A middle aged alcoholic





In him, as in NIB, the observation of abnormal glycogen storage test values in the presence of normal bromsulfalein findings is striking.

**PATIENT WRI**—A young alcoholic cirrhotic with surprisingly normal chemical findings despite highly abnormal clinical and histological findings. It is interesting that the abnormal glycogen storage test and a barely abnormal icterus index were the only chemical reflections of a major alcoholic debauch.

**PATIENT JOY**—A middle aged male in the same category as NIB.

*Chronic (viral) Hepatitis.* The data on these men are included in another article devoted to a discussion of this pathological entity. Suffice it to say here that for the most part the glycogen storage test findings correlate well with other laboratory observations.

**Discussion.** The data here reported are representative of more than 2,000 individual observations obtained over a period of 5 years. It is our very strong conviction that one contributes nothing to clinical or laboratory medicine by adding new, inconclusive procedures to an already badly confused field. It is our hope and belief, for the following reasons, that the glycogen storage test does not fall in this category:

1. Any panel of tests of liver function should include some procedure which provides a clue to the carbohydrate metabolic activity of the liver. The glycogen storage test, as contrasted to procedures based upon the oral or intravenous administration of sugars, supplies essentially unequivocal information, in that the initial elevation of blood sugar, in response to adrenalin, can relate only to pre-existing hepatic

glycogen. It is theoretically possible that muscle glycogen, broken down to lactate in response to adrenalin, and then re-synthesized to hepatic glycogen might affect the shape of the curve if one followed it over a 2 to 3 hour period. This is of only academic interest insofar as the present report is concerned.

2. From the representative data here reported, it is apparent that the glycogen storage test may supply evidence of hepatic abnormality which is not supplied by other function tests. It is equally obvious that the glycogen storage test does not in any sense replace such standard procedures as the bromsulfalein and the cephalin cholesterol flocculation tests. It is again emphasized that the reliability of the test is dependent upon a careful standardization of conditions during its performance.

**Summary.** The blood sugar response to a standard intramuscular dose of adrenalin in the normal adult, under standard conditions, is predictable and dependable. This response is appreciably diminished in patients with acute and chronic liver damage, but reverts to normal with its improvement. The procedure may therefore properly be used as one of a "panel" of tests of liver function.

Hemorrhage from esophageal varices has recently been observed in one man some hours post-adrenalin. It may be that the association of splenomegaly and esophageal varices should be regarded as a contraindication to the procedure.

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# THE EFFECT OF BENZOIC ACID AND CARONAMIDE ON BLOOD PENICILLIN LEVELS AND ON RENAL FUNCTION\*

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SINCE 1943, various substances which will interfere with the tubular excretion of penicillin have been studied. Diodrast<sup>2,12,13</sup> and para-amino hippuric acid<sup>4,11</sup> have proven to be effective but must be given by continuous intravenous administration in large doses and are not clinically practical for this reason. Benzoic acid<sup>8,9,15</sup> sodium benzoate, and more recently caronamide†<sup>3,5,6</sup> have been used orally. With the exception of caronamide all are thought to act by blocking the tubular excretion of penicillin. Bronfenbrenner and Favour<sup>9</sup> reported 4 to 7-fold enhancement of blood penicillin levels when benzoic acid was given orally but found that severe fluid and salt restriction was necessary to accomplish this. Spaulding, Bondi, and Early<sup>15</sup> also reported favorably on the use of this substance for enhancing blood levels of orally administered penicillin. Boger and Baker<sup>7</sup> have recently reported failure to increase blood penicillin levels by the use of benzoic acid when fluid and salt intake was not restricted.

In the last few months, several papers have appeared which deal with the clinical use of caronamide.<sup>7,10</sup> All have reported the effectiveness of this

substance in increasing blood penicillin levels. Rather exhaustive renal studies in dogs have been carried out by Beyer,<sup>5</sup> who has been unable to find any evidence of renal damage from this drug. Boger and Baker<sup>7</sup> have reported that the administration of caronamide will increase the blood penicillin levels by about 8-fold and that this effect can be achieved at any dose level of penicillin.

To determine the clinical usefulness of such a drug two questions must be answered. (1) When administered orally over a long period in amounts that will be tolerated by the patient, does the drug effectively increase the blood penicillin level? (2) Under these circumstances, does the drug produce any renal damage? As far as caronamide is concerned, the question of renal damage seems to have been well answered in the negative. There is no available information of this sort concerning benzoic acid. This report is presented in an effort to answer the above questions.

**Methods:** The penicillin blood levels were determined by the reductase method of Reid and Brewer.<sup>14</sup> This method gave good reproducible results within the range of blood con-

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† "Staticin" Caronamide (4 Carboxyphenylmethanesulfonamide) was furnished through the courtesy of Sharpe and Dohme, Inc., Philadelphia, Pennsylvania.

centrations found in our subjects and has the advantage over other methods in that there is a sharp endpoint and one that is easy to read. The method was checked by repeated determination of known concentrations of penicillin in saline and in serum and was also checked against the Rammelkamp method. Under all these circumstances it was found to be adequate. All determinations were carefully controlled for the presence of the so-called "antibutyl factor".<sup>11</sup> Determinations were usually made within a few hours of the time the blood sample was withdrawn and when this was not feasible the serum was promptly separated and frozen. Blood urea nitrogen levels were determined by the method of Archibald<sup>1</sup> and the endogenous creatinine clearances were determined by the usual Jaffe reaction using a tungstate filtrate.

#### Plan of Study and Results. Benzoic Acid—Nine patients in the Intensive

Treatment Center (7 with early syphilis and 2 with central nervous system syphilis) were selected as subjects for this study. All were free from evidence of any other disease, particularly renal or hepatic, except 1 who showed consistently a diminished creatinine clearance without other evidence of disease. At the start it was thought that the patients could be studied while receiving the routine treatment of mapharsen, penicillin and bismuth but it soon was discovered that mapharsen caused a sharp, though temporary, reduction in renal function. Consequently the patients used in this experiment received only penicillin. No attempt was made to limit either fluid or food

TABLE 1.—BLOOD PENICILLIN LEVELS AND BLOOD UREA NITROGEN LEVELS IN PATIENTS RECEIVING 12 GM. OF BENZOIC ACID DAILY

Patient	Average Blood Penicillin Level Units/cc		Average Blood Urea Nitrogen Mgs./100 cc		Creatinine Clearance cc/min.	Final
	before Benzoic Acid	after Benzoic Acid	before Benzoic Acid	after Benzoic Acid	Initial	
D.R.	0.20	0.17	17	11	57	60
S.V.	0.20	0.10	11	18	82	87
Man.	0.07	0.20	11	18	92	99
Mar.	0.08	0.23	28	27	92	131
A.T.	0.11	0.10	18	9	70	69
An.	0.16	0.09	21	19	144	145
L.H.	0.22	0.28	23	31	115	121
J.V.	0.12	0.14	18	13	94	103
H.P.	0.04	0.09	17.5	11.7	129	82

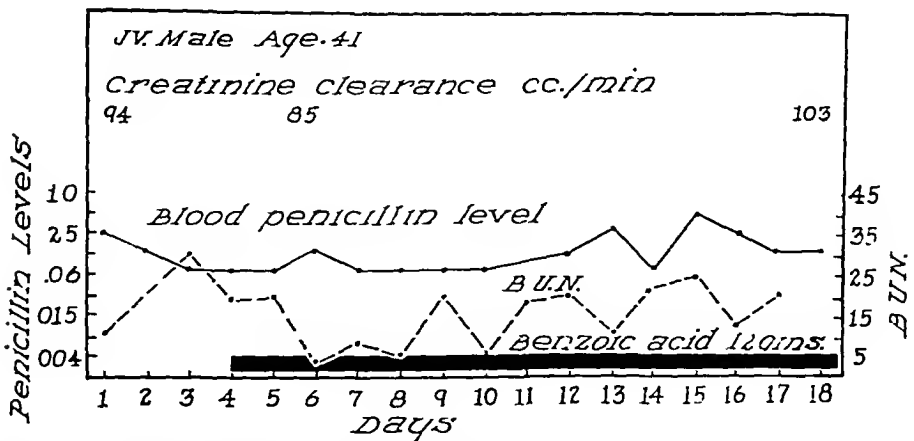


Chart 1.—The blood penicillin level, blood urea nitrogen, and creatinine clearance of 1 patient who received 12 gm. of benzoic acid per day for 14 days. None of these was significantly different from control levels.

intake during the experimental periods. Crystalline penicillin G in saline was administered intramuscularly to all subjects in doses of 30,000 units every 3 hours. The control period was started after the subjects had received penicillin for 18 to 24 hours. Penicillin and blood urea nitrogen levels were determined daily one and one-half hours after the most recent dose of penicillin and the endogenous creatinine clearance was measured at the beginning and end of the experimental period and in some cases on the fifth day as well. After a 4-day control period, 12 gm. of benzoic acid divided into 8 doses was administered orally for the next five

(Chart 1). The blood urea nitrogen levels showed no consistent alteration beyond the rather wide variation from day to day that is to be expected when the patient is receiving the usual hospital diet. In no case did the endogenous creatinine clearance show any significant change from the control period. Routine urinalysis also failed to show any abnormality.

*Caronamide.* Twelve patients (5 luetics and 7 convalescent from various infectious diseases) were used as subjects. All were free from evidence of renal or hepatic disease. Blood penicillin levels were determined daily at 1 and 3 hours after an injection of peni-

TABLE 2.—BLOOD PENICILLIN LEVELS IN PATIENTS RECEIVING CARONAMIDE DAILY

Patient	Control Period		Dose Caronamide Grams/24 hrs.	While receiving Caronamide for					
	Penicillin/cc. blood			24 hrs.	48 hrs.		72 hrs.		
	Av. 1 hr.	Av. 3 hrs.		Penicillin/cc. blood at					
				1 hr.	3 hrs.	1 hr.	3 hrs.	1 hr.	3 hrs.
Gi.	0.5	0.12	24	4.0	1.0	16.0	1.0	16.0	2.0
O.	0.5	0	24	0.5	0.12	2.0	1.0	2.0	1.0
Ge.	0.25	0.09	24	0.5	0.06	1.0	0.5	2.0	0.25
Du.	0.18	0	24	1.0	0.25	0.12	0.06	0.5	0.06
J.B.	0.31	0	20	4.0	0.5	1.0	0.12	2.0	1.0
C.P.	0.5	0	20	1.0	0.12	0.25	0	0.25	0.06
Hic.	0.5	0.09	16	0.5	0.12	0.5	0.5	2.0	0.5
D.D.	0.25	0.06	16	0.5	0.06	0.5	0.12	1.0	0.25
Ke.	0.25	0	12	1.0	0.06	1.0	0.12		
St.	0.09	0	12	0.12	0.06	1.0	0.12	0.5	0
Sm.	0.12	0	12	0.06	0	0.12	0	0.5	0
Carl.	0.12	0	12	0.06	0	0.12	0	0.25	0

days to all the subjects except one, who received this amount of benzoic acid for 14 days.

The results of these observations are summarized in Table 1. It may be seen that of the 9 subjects, there was some increase in the average blood penicillin levels in 3, no essential change in 3, and a lower average level in 3. Individual charts, however, show that the changes were not constant from day to day and that there was really little essential change over the control level. One Patient (J. V.) did show about a 2-fold enhancement but only after receiving benzoic acid for 7 days

cillin. All subjects received aqueous penicillin intramuscularly at 3 hour intervals, but did not necessarily receive the same dose. Each individual subject, however, did receive the same amount of penicillin throughout the experiment. After a 2 day control period, the patients were given caronamide in doses varying from 12 to 24 gm. per day in 8 equal doses for the next 3 days. In addition to these short term studies, combined penicillin and caronamide therapy was maintained for at least 1 month in 2 subjects. Each patient received 24 gm. or more of caronamide per day. Penicillin levels

were determined 2 or 3 times a week. The purpose of this part of the experiment was not so much to determine enhancement of the blood penicillin levels as to evaluate the feasibility of administering caronamide over a long period.

The results of the caronamide study are shown in Table 2. It may be seen that doses of 12 and 16 gm. per day failed, in most cases, to alter the blood penicillin level significantly. Doses of 20 to 24 gm. per day, however, gave

this patient it became necessary at times to increase the penicillin dosage. Therefore, the actual increase in blood penicillin levels cannot be ascribed wholly to caronamide. We were particularly interested in one phenomenon, shown in Chart 3. After administration of 24 gm. of caronamide per day for 8 days, the penicillin levels fell off rather sharply and symptoms recurred. When the dose of caronamide was increased to 32 gm. per day the blood penicillin levels became stable and

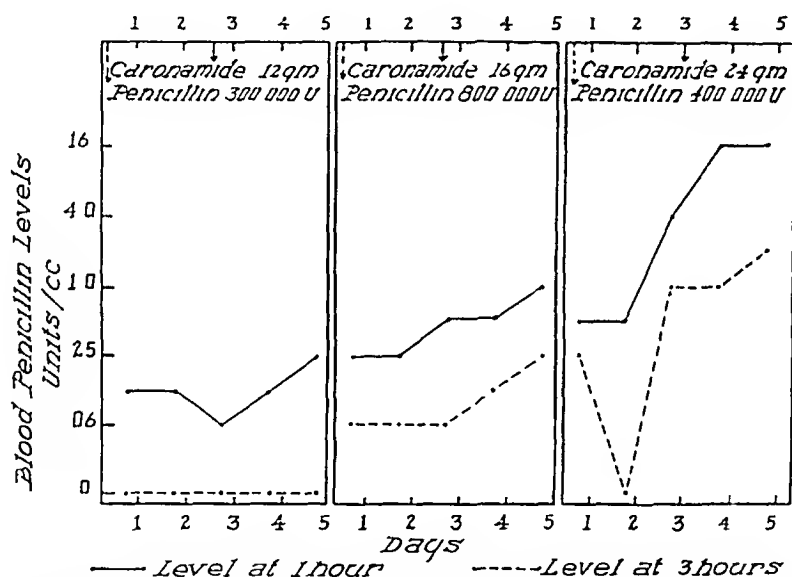


Chart 2—The effect of various doses of caronamide on the blood penicillin level of individual subjects. The arrows indicate the time at which the administration of penicillin and caronamide, respectively, was begun.

4 to 16-fold increases in the blood penicillin level (Chart 2). It is of interest to note that in a number of cases the blood penicillin levels were higher 48 and 72 hours after beginning caronamide than at 24 hours. It is noteworthy too that in many cases caronamide produced a greater relative increase in the blood penicillin level at 3 hours than at 1 hour after injection.

The results in 1 of the 2 patients with subacute bacterial endocarditis are shown in Chart 3. In the treatment of

remained so during the rest of the time that caronamide was being administered.

This patient, who died on his 96th hospital day, received a total of 1650 gm. of caronamide in 58 days. At autopsy the kidneys were grossly normal and on section showed no abnormality that could be attributed to the drug. This suggests that this drug even in large doses for long periods does not damage the kidneys.

**Discussion.** From the above data, it is evident that the administration of 12 gm. of benzoic per day has little effect in enhancing the blood penicillin levels. It is true that this quantity is not as great as others have used, but preliminary observations convinced us that this dosage was about all that the usual patient would tolerate over a long period of time. Even with this relatively small amount, about one third of the patients complained of gastric burning and some anorexia. It is entirely possible that had salts and

acid over periods up to 14 days and conclude that this drug, in the doses used at least, does not damage the kidney.

Caronamide, on the other hand, when given in doses of 20 gm. a day or more appears to be an effective agent for increasing the blood penicillin levels, and has the additional advantage that no limitation of salt or fluid seems to be necessary. More important, perhaps, is the ability of caronamide to prevent the rapid decline of blood penicillin levels between injections

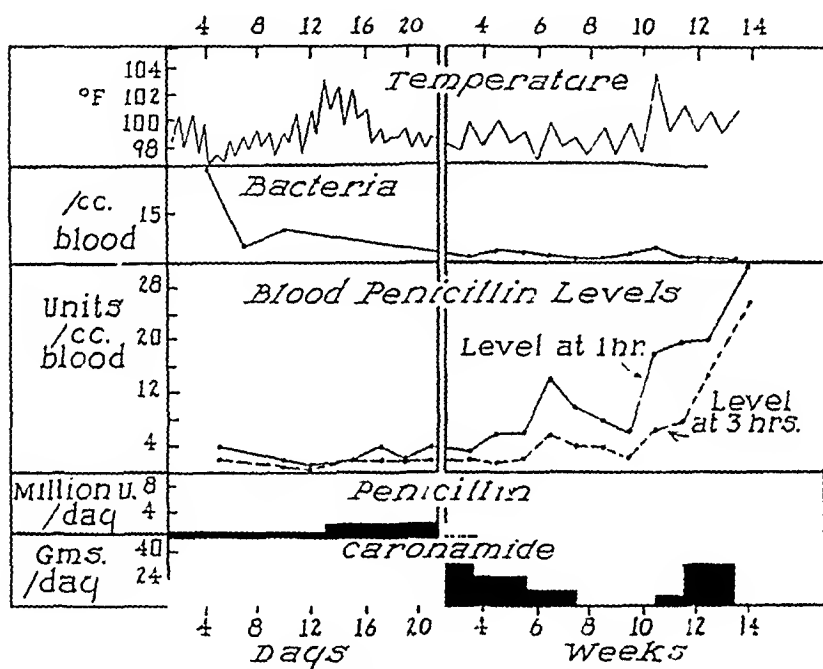


Chart 3.—Summary of data obtained in 1 patient with subacute bacterial endocarditis. In that portion of the chart designated by weeks, the amount of caronamide and penicillin administered is indicated as the average per day for that week.

Note the sharp pre-mortal rise in the blood penicillin level.

fluids been strictly limited, the levels might have been higher but such restriction over several days is difficult at any time and in the presence of a febrile illness would be undesirable. Boger and Baker<sup>7</sup> used up to 24 gm. of benzoic acid per day and demonstrated no increase of the blood penicillin levels. We were unable to demonstrate any evidence of renal impairment during the administration of benzoic

during intermittent parenteral administration.

We have found this drug to be ordinarily well tolerated by the patients. About one-quarter of the patients complained of mild anorexia which seemed to correlate best with the number of pills they were taking. No severe reactions attributable to caronamide were observed.

We did not determine the blood or



urine caronamide levels of any of the subjects in this series. Such measurements may prove to be useful for adjusting caronamide dosage. We believe, however, that the alteration of the blood penicillin level gives a good index as to the effectiveness of the caronamide dosage and at the same time offers more useful clinical information than the caronamide level. This is well illustrated in Chart 3.

It has been stated by a number of investigators that in the treatment of most of the infectious diseases that respond to penicillin, higher levels are easily obtained by simply increasing the dose of penicillin and that the various enhancing agents are of no great clinical value. In general, we are in accord with this view. However, in certain diseases, particularly subacute bacterial endocarditis and those infections caused by an organism with a

relatively high resistance to penicillin, caronamide is a valuable adjuvant to therapy, and combined penicillin and caronamide will result in higher and better sustained levels than can be obtained by the use of any reasonable dose of penicillin alone.

**Summary and Conclusions.** 1. In the presence of normal fluid and electrolyte intake, benzoic acid was ineffective in enhancing the blood penicillin level. In doses of 12 gm. per day for periods of 14 days or less no measurable renal damage was observed.

2. Caronamide in suitable dosage is an effective agent for increasing and prolonging the blood penicillin concentration.

3. One patient received 1650 gm. of caronamide and showed no damage to the kidneys when these were examined post mortem.

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# PROGRESS OF MEDICAL SCIENCE

## RADIOLOGY

UNDER THE CHARGE OF

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AND

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### THE NORMAL ROENTGENOGRAM OF THE CHEST IN INFANTS AND CHILDREN

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THE determination of normal in roentgenograms of the chest in infants and children is difficult because of the constantly changing appearance of the chest owing to the growth and development of the child. By definition, normal means "according to or constituting an established norm, rule or principle." In deciding what is to be the standard of normal in an infant or child, proper latitude must be provided to include those normal variations in morphology which are secondary to the normal growth and development of the child and which are without significance in the diagnosis of disease.

In addition to the effect of growth and development on the roentgenogram of the chest there are also obvious mechanical problems associated with obtaining roentgenograms of the chest in infants and children. In the adult in most cases it is possible to obtain the patient's co-operation, so that roentgenograms of the chest are fairly uniform with respect to the phase of respiration and the position of the chest on

the roentgenogram. With children, on the other hand, even with care in roentgenography it is difficult to obtain uniform results. Roentgenograms may be made in almost any phase of respiration; position is difficult to control and rotation of the patient may produce apparent changes in the roentgenogram, making interpretation difficult. Even with restraining devices motion is difficult to control. Clothing and hair braids, muscle and soft tissue shadows seem to be more confusing in the interpretation of roentgenograms of the chest in infants and children than in adults.

Interpretation of the roentgenograms of the chest in infants and children depends on a consideration of these factors that will influence the appearance of the roentgenogram but the diagnosis of normal is not directly related to these factors, except that they may act to obscure and confuse the correct diagnosis. The roentgenographic diagnosis of normal depends on the recognition of a progression of changes which take

place in the healthy child, which are evident on the roentgenogram of the chest and which are not associated with disease.

In order to determine what should be included in the range of normal in infants and children and also to determine, if possible, the time, nature and degree of any changes in the roentgenographic appearance of the chest that might be associated with their growth and development, I reviewed the thoracic roentgenograms of several hundred children. These children had no symptoms referable to the chest or evidence suggesting pulmonary disease. All these roentgenograms had previously been reported as negative.

In reviewing these roentgenograms I tried to correlate the roentgenographic findings with the age of the infant or child. For the purposes of interpretation, the structures of the chest represented on the roentgenogram were divided into: 1, the bones of the thoracic cage and shoulder girdle; 2, the aorta, pulmonary vessels and mediastinal shadow, exclusive of the thymus; 3, the cardiac silhouette; 4, the bronchovascular markings; 5, the diaphragm; 6, the lungs; and 7, the thymus. The age groups of these infants and children were also arbitrarily divided into: 1, newborn through the first month; 2, 1 month through 12 months; 3, 1 year through 3 years; 4, 4 through 7 years; 5, 8 through 12 years. These various age groups were not determined until after the roentgenograms of the chest had been reviewed and then the separation into these various age groups seemed to be a rather natural procedure in view of the findings as noted on the roentgenograms.

#### BIRTH THROUGH THE FIRST MONTH.

In most of the roentgenograms of the chest in newborn infants the ribs are perpendicular to the spinal column and encircle the thorax at the same level

that they leave the spinal column. This varies somewhat with the phase of respiration and occasionally the more adult type appearance is seen with anterior downward slope of the ribs. The body of the scapula and the acromion process, as well as the clavicles, are fairly well formed, although the coracoid process is not well developed. The epiphysis of the head of the humerus can be seen as a small, rounded area of increased density between the upper end of the shaft of the humerus and the glenoid fossa of the scapula.

The shadow of the aorta is not seen. The pulmonary vessels are also very difficult to identify. The mediastinal shadow, which seems to be proportionately wide, is produced by the thymus and the cardiac silhouette.

Cardiac size and shape are extremely variable in newborn infants. Farrell<sup>2</sup> has classified the heart shape into 4 groups: 1, long narrow; 2, broad apical with a narrow base; 3, broad apical with a broad base; and 4, round globular. The second and third types make up the great majority of cardiac contour types in infants. Determination of cardiac size in infants is not wholly satisfactory, possibly because the phase of respiration affects the cardiac contour proportionately more in newborn infants than later in life. Weymuller, Bell and Krahulik<sup>3</sup> stated that accurate measurement of the cardiac shadow on the roentgenogram is technically impossible because of the great individual variation in cardiac size and contour. Farrell<sup>2</sup> measured the heart size in newborn infants and found that the cardiothoracic index was 0.55, only 0.05 greater than that taken to be normal in adults. Most investigators are agreed that although there is probably some cardiac enlargement the first and second days of life, there is probably a fairly regular tendency toward reduction in the size of the heart as mani-

fested on the roentgenogram after the second day.

In my experience the bronchovascular markings were proportionately smaller and less distinct in the newborn infant than in older persons.

The diaphragm assumes varied contours peculiar to the individual. It may be domeshaped, flat or even conical. Caffey<sup>1</sup> stated that the conically shaped diaphragm tends to be present more frequently early in life than later but the shape of the diaphragm, once established, does not change appreciably during growth to adulthood. Proportionately the extent of diaphragmatic motion is about the same in infants and children.

The lungs of stillborn infants are seen as a homogeneous dense shadow on the roentgenogram of the chest. In the living infant at birth, air enters the atelectatic lung, causing expansion of the alveolar spaces. In some cases the process of expansion is incomplete and atelectatic areas are noted in the roentgenogram of the chest. Wasson<sup>8</sup> has pointed out that on the one hand these may be small patches of increased density in the lung involving only small regions of parenchyma or on the other hand whole lobes may be unexpanded. The time required for complete expansion of the lungs has been estimated by Wasson<sup>8</sup> to vary from 5 minutes to 2 weeks. Solis-Cohen and Bruck<sup>6</sup> reported an incidence of 4% of cases of newborn infants with atelectasis. Weymuller, Bell and Krahulik<sup>9</sup> reported 1 infant in 25 who presented roentgenographic evidence of incomplete expansion of the lungs. The bases of the lungs are probably the last portions of the lungs to become completely aerated. Atelectasis due to incomplete expansion of pulmonary tissue is probably not often seen after the first few days of life. Wasson<sup>8</sup>, and Weymuller, Bell and Krahulik<sup>9</sup> described linear markings in the lungs of newborn infants

that are fairly prominent and can be traced well out to the periphery of the lungs. These markings are seen rather frequently, but disappear after the first few weeks of life. The reason for their presence is not entirely clear. They may be associated with incomplete expansion of the lung but their continuity with hilar shadows suggests that they may be related to some adjustment in the pulmonary circulation which takes place early in life.

Farrell<sup>2</sup> reported the presence of a roentgenographically recognizable thymus in measurable chests in a little less than one third of his cases of newborn infants. It is probable that roentgenograms made in the expiratory phase would demonstrate a much higher percentage of thymuses. The incidence of a thymus in newborn infants depends on what is interpreted as thymic shadow. In my experience there is a recognizable thymic shadow in practically all newborn infants, although there is great variation in its size and shape. Classifications devised to describe the numerous thymic outlines become too complicated because of the protean character of the organ.

ONE MONTH THROUGH 12 MONTHS. From 1 month through 12 months the thoracic cage does not change appreciably. The ribs in most cases are similar in position to those of the newborn infant. The capital epiphysis of the humerus grows in size and presents an oval appearance.

The aorta is not visible because on leaving the heart it passes directly upward, backward and down. The pulmonary vessels may be seen. If measured they are found to proportionately larger with respect to the size of the chest than later in life.

The cardiac size gradually decreases during the first year of life, and when the child is 1 year old the ratio of cardiac size to chest size is approxi-

mately that of the adult. Cardiac size is probably in normal ratio after 6 months.

The peribronchial and perivascular markings become better defined during the first year, but they are less noticeable at this time than they are during the next year of life. The lungs in the region of the cardiophrenic angles are still relatively clear, and the peribronchial and perivascular markings that can be seen are more or less confined to the immediate region of the hilus of the lung.

The diaphragm in this age group is not remarkable. The diaphragmatic level varies between the eighth and the tenth ribs posteriorly, depending on the degree of inspiration and on individual constitutional structure of the child and the characteristic appearance of the diaphragm.

The growth in length of the child gives the lungs a more adult appearance. There are generally no areas of fibrosis or calcification encountered in the lungs in infants of this age.

The thymus is usually still present if it was seen roentgenologically at birth. Wasson<sup>7</sup> has stated that the thymus continues to enlarge up to 1 year of age, after which it begins to decrease in size. My experience has been that most of the thymuses that are seen at birth are smaller by the time the infant is 1 year old. Perhaps this is due to a difference in the rate of growth of the infant's chest and the thymus, with the chest growing faster than the thymus.

**ONE YEAR THROUGH 3 YEARS.** In the average infant, the ribs begin to shape downward anteriorly between 1 and 2 years of age, and usually by the time the child is 2 years old the ribs have reached the relative position and shape they will maintain throughout life. The clavicles and scapulae are well formed. The epiphysis for the greater tuberosity of the humerus appears near the age of

2 years, and the proximal end of the humeral shaft acquires a pointed or conical shape. The aortic shadow is still not seen. The mediastinal shadow, composed of the bases of the great vessels and the thymus, is narrower, partly owing to growth in length of the chest and partly to regression of the thymus. The pulmonary vessels are still slightly larger in proportion to the entire chest but between the second and third years this disproportion disappears.

The cardiac silhouette has assumed its normal relative proportion to the rest of the chest, and although the shape varies with the individual there is nothing remarkable about it.

During the period between 1 and 3 years of age the child usually learns to walk and spends relatively more of his time on his feet. Beginning at 1½ years of age there was noted an increase in the bronchovascular markings in the roentgenogram of the chest. The appearance of the bronchovascular markings on the roentgenogram may be influenced by: 1, the amount of overlying soft tissue; 2, the phase of respiration; 3, the exposure factors used in obtaining the roentgenogram; and 4, the amount of connective tissue present in the peribronchial and perivascular tissues. If all these factors are taken into consideration there is still a relative increase in the prominence of the bronchovascular markings between 1½ and 3 years. It has been suggested that there may be some disproportion in growth between the bronchi and vessels and the parenchyma of the lung. Wasson<sup>7</sup> has stated that there is a relative increase in the bronchovascular markings from birth to 3 years of age. In my experience there is a gradual increase in these markings between 1½ years and 3 years. In the 3 year and 4 year age groups they are most marked, being proportionately more evident than in

the adult, except for the aged. Maresh and Washburn<sup>3</sup> pointed out that in follow-up studies of infants and children the variation in the prominence of bronchovascular markings is as much a part of individual changes in growth and development as differences in size and shape of the cardiac silhouette. In the opinion of these authors, each child establishes his own normal for the appearance of the hilar shadows and pulmonary markings soon after birth, and these characteristics are maintained throughout life without any consistent relation to the amount of infection that may be present in the accessory sinuses of the head.

The diaphragm in this age group was not remarkable. The average diaphragmatic level with respect to the ribs was between the ninth and tenth posterior ribs. In the roentgenograms reviewed for this age group the diaphragm appeared to be flatter and less dome-shaped. There was no apparent explanation for this fact.

The pulmonary parenchyma is not remarkable in this age group, and in the average child no pulmonary parenchymal shadows are seen on the roentgenogram.

In my experience the shadow of the thymus is usually smaller at 1 year of age than at birth, and it decreases in size until by 3 years of age it has disappeared. Very little of the shadow of the thymus remains to be seen at 2 years of age. Wasson stated that the shadow of the thymus in children usually disappears by the twenty-sixth or twenty-eighth month. Mosher, Macmillan and Motley<sup>4</sup> reported that roentgenograms of the chest in 2,344 children from 1 to 16 years of age demonstrated thymic shadows in 7.5%. Of these, 20% were seen at 1 year of age, 23% at 2 years, 20% at 3 years and 10% at 4 years, with the remainder more than 4 years of age.

**FOUR THROUGH 7 YEARS.** The bones of the thoracic cage and the shoulder girdle do not show any appreciable change early in this age group. The epiphyses of the head of the humerus and the greater tuberosity of the humerus begin to fuse. The ribs, clavicles and scapulae show the evidences of growth that may be expected. The cortex is somewhat thicker and the trabeculation of medullary bone is more well defined.

In the average child the aortic knob is not seen. The pulmonary vessels are proportional to the size of the chest.

The cardiac silhouette is of normal shape and size.

The bronchovascular markings in the 3 year to 4 year age group, which seem to be more prominent and proportionately heavier than in older children and adults, gradually become less marked and assume a normal adult proportion as the child reaches the 5th to the 7th year.

The appearance of the diaphragm is not significant in this group.

The pulmonary parenchyma occasionally shows a small area of fibrosis or a tiny area of calcification in normal children in this group between 4 and 7 years. It may be argued that a roentgenogram of the chest that demonstrates fibrosis or calcification in a child is not normal. On the other hand, such findings in an otherwise healthy, normal child without any previous history of recognized disease are rather difficult to explain, unless they can be classified within the limits of normal.

The thymic shadow in the normal child has disappeared by this time.

**EIGHT THROUGH 12 YEARS.** Probably very few roentgenologists would agree now with a statement made over 25 years ago that "the chest of a child (from 6 to 10 years of age) from a roentgenologic standpoint is subject to such wide variation within normal limits as to be beyond the possibility of

exact description<sup>5</sup>." With present-day equipment it is possible to obtain roentgenograms of a quality that makes exact description easier. By the time the child has reached 8 years of age, the relative proportions of the bones of the thoracic cage, the heart, lungs and other structures have reached a ratio which is relatively normal in proportion to the chest as a whole. The aortic knob can frequently be identified. Areas of calcification and

fibrosis in the lung are not uncommon and calcification in the hilar nodes is also fairly frequent.

**Conclusions.** The roentgenograms of the chests of infants and children present somewhat different findings from those of adults, and the range of normal is wider in infants and children than in adults. The variants of normal in infants and children are associated with the growth and development of the child.

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# THERAPEUTICS

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## FOLIC ACID AND ANTAGONISTS IN NEOPLASTIC DISEASE

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ATTEMPTS to affect the course of neoplastic disease in animals and man by the internal use of chemical agents have met with limited, though measurable success. Chemotherapeutic agents of demonstrable activity include arsenicals, benzol, urethane, and nitrogen mustards. These may be regarded as effective by virtue of a selective injury to proliferating cells (see reviews by Karnofsky<sup>12</sup>, Gellhorn and Jones<sup>28</sup>). The mechanism underlying selective damage may be related to actions against basic metabolic functions common to all cells. Nevertheless, specific susceptibility of proliferating cells to such derangements could result from their greater dependence on synthetic mechanisms to supply the needs of growth and cell division. Alternatively, the complex mechanisms underlying cell division may involve unique biochemical processes exhibiting specific susceptibilities to the actions of chemical agents. Accordingly, non-dividing

cells are less affected. Similar considerations based on the relatively rapid rate of growth characteristic of many malignant tissues have stimulated investigations into the possible relationship between deficiencies of vitamins and the course of neoplastic diseases<sup>10</sup>. The requirements of rapidly growing malignant tissues for accessory growth factors may be relatively great, thus rendering them susceptible to retardation or even inhibition by vitamin deficiencies induced in the host. Since vitamins are known to be key components of co-enzyme-prosthetic groups of enzymes<sup>10,17</sup>, reductions of amounts available to malignant tissues may have the same chemotherapeutic result as the agents mentioned above.

Evidence specifically relating vitamins and malignant growth was considered unimpressive as recently as 1944 in a detailed review of the subject by Burk and Winzler<sup>10</sup>. Since that time, however, new investigations have demon-

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strated the potential chemotherapeutic value of deficiencies of certain vitamins of the B-complex. Of specific interest to the present review are studies suggesting the dependence of the growth of a variety of tumors on the utilization of folic acid. These studies followed the elucidation of the structure of folic acid and the subsequent synthesis of a series of closely related structural analogs which act as specific antagonists of folic acid. This review deals with the current knowledge of the latter substances, not as regards proven usefulness as chemotherapeutic drugs, but concerning the demonstration that anti-metabolites can inhibit growth of tumors.

**FOLIC ACID AS A VITAMIN.** In order to understand the function of folic acid in the development of neoplastic tissues, it is essential to consider the manifestations of folic acid deficiency in normal tissues. It is, therefore, of value to review briefly the current status of folic acid in nutrition of various organisms. Only some of the landmarks in the history of the vitamin will be mentioned. For more detailed information the reader is referred to excellent reviews of others<sup>1,4,14,41,68,90</sup>.

The name "folic acid" was first applied to concentrates of spinach containing an active principle required for the growth of certain microorganisms<sup>59</sup>. The vitamin has been isolated in pure form from liver<sup>65,78</sup> and from yeast<sup>7</sup>. Proof of its structure was obtained by the synthesis of pteroylglutamic acid (PGA)<sup>35,88</sup>. Two conjugates of the vitamin containing varying numbers of glutamic acid residues have been isolated from natural sources, namely, pteroyltriglutamic acid<sup>36</sup> (see reviews by various authors<sup>1</sup> and by Jukes and Stokstad<sup>41</sup> for proof of structure) and pteroylheptaglutamic acid<sup>66,67</sup>.

The requirements of many lactic

acid bacteria as well as other species for PGA have been well established (see review by Jukes and Stokstad<sup>41</sup>). The growth of a ciliated protozoon has also been found dependent on PGA<sup>43</sup>. Among insects larval development of the mosquito *Aedes aegypti* is possible in the absence of folic acid but pupation does not occur<sup>29</sup>. The larval development and pupation of the flour moth, the flour beetle, and the meal worm, fail in the absence of adequate levels of PGA in the diets of these insects<sup>23,30</sup>.

Studies on folic acid requirements of birds and mammals have revealed proliferating tissues to be selectively dependent for normal activity on the presence of adequate levels of the vitamin. Thus a cardinal feature of folic acid deficiency in warm-blooded organisms is a derangement and depletion of myelopoiesis and erythropoiesis. Inadequate levels of the vitamin in the diet of chicks lead to anemia, leukopenia, and thrombocytopenia, as well as poor feathering and inadequate growth<sup>11,34,65</sup>. Rats receiving purified diets, supplemented by sulfonamide drugs to suppress vitamin-synthesis by intestinal flora, develop anemia and granulocytopenia as the result of inhibition of myelopoiesis and erythropoiesis. Such lesions respond promptly to the administration of PGA<sup>18,62,75,96</sup>. In monkeys the feeding of diets low in PGA leads to granulocytopenia, megaloblastic erythropoiesis with attending macrocytic anemia, and various disorders of the digestive tract with lesions of the oral mucosa and diarrhea<sup>16,47,91,92</sup>. The satisfactory response of the deficiency-disease in monkeys to administration of PGA has its counterpart in various human macrocytic anemias which are amenable to therapy with the vitamin. Successes achieved in alleviating signs and symptoms of sprue, macrocytic anemias of infancy and pregnancy, and

megaloblastic anemias refractory to parenteral liver therapy, as well hematological remissions produced in pernicious anemia, have evidenced the nutritional importance of folic acid as a factor for normal hematopoiesis in man (see reviews<sup>4,14,41,68,90</sup>).

Conjugated forms of PGA, pteroyltriglutamic acid, pteroylheptaglutamic acid, and pteroyldiglutamic acid, appear to be as effective as PGA in alleviating folic acid deficiency in birds and mammals<sup>5,15,36,79,96</sup>. Presumably the activity of the conjugates results from enzymatic hydrolysis of the polyglutamyl portions with release of free PGA. Enzymes designated as "conjugases" have been found in a variety of tissues capable of releasing PGA from the more complex conjugates<sup>6</sup>.

The administration of pteroyldiglutamic acid, pteroyltriglutamic acid, and pteroylheptaglutamic acid in normal humans is followed within a few hours by increased levels of free PGA in blood and urine<sup>40,73,81</sup>. The concentrations achieved approximate those following the administration of molar equivalent doses of unconjugated PGA.

**FOLIC ACID ANTAGONISTS.** After it had become evident that PGA is an essential metabolite for the maintenance of myeloid and erythroid tissues, it was logical to assess its role in neoplastic tissues, especially those of hematopoietic origin. While some success has been achieved in preventing the growth of at least one experimental tumor by dietary restriction of folic acid (see below), investigations in this field have been largely concerned with the chemotherapeutic potentialities of potent antagonists of PGA. The possibilities inherent in the use of analogs to antagonize the biological actions of vitamins were first established by Woods<sup>91</sup> in the classic demonstration of antagonism between sulfanilamide and para-aminobenzoic acid

in microorganisms. A satisfactory generalization of the actions of metabolite antagonists has been made by Wooley<sup>95</sup>. "... a metabolite functions by first combining with a particular cellular unit which is usually regarded as an enzyme or possibly some other specific protein. . . . Now, in order for the first step to occur, the metabolite must possess certain structural features and the firmness of combination with the protein is determined in part by these. A similarly constituted compound is able to undergo this combination, but since its structure is not identical with that of the metabolite, its firmness of union will be different. The conjugate of analog and protein is, however, a new and foreign compound and is unable to proceed through the rest of the cycle of reactions. Like the fabled dog in the manger the analog denies the organism the use of the metabolite and thus creates a deficiency of the latter."

The first analog of PGA found to antagonize the vitamin in mammals was a crude product synthesized to contain a methyl-substituted pteroylg glutamic acid, referred to as "X-Methyl folic acid"<sup>24,25</sup>. When the agent was added as a supplement to deficient diets in concentrations several thousandfold greater than that of PGA, characteristic signs of PGA-deficiency in mice, chicks, and rats were accelerated in appearance and enhanced in severity. The syndrome was readily prevented or successfully treated by administration of elevated levels of PGA. In later studies with mice<sup>89</sup> and pigs<sup>12,32</sup>, species relatively resistant to deficient diets, supplements of X-methyl folic acid caused hematological lesions which readily responded to treatment with the vitamin. In pigs the signs of the deficiency resembled sprue in the appearance of megaloblastic anemia, leukopenia, and diarrhea.

Many additional analogs of PGA have been prepared exhibiting antagonisms toward the biological actions of folic acid in one or more microorganisms, birds, or mammals. Of present interest is a related series of antagonists which was introduced by the synthesis of 4-aminopteroylglutamic acid (4-amino-PGA<sup>74</sup>). The series is characterized by the replacement of the 4-hydroxyl of PGA with an amino group with varying modification of the remainder of the molecule. Observations of the effects of 4-amino-PGA in mice, rats, and chicks proved it toxic and even fatal within a few days after administration in diets in concentrations which were approximately equivalent to the amounts of PGA present<sup>28,64,83</sup>. Simultaneous administration of PGA provided only limited protection against the toxic actions of the congener.

The potency of 4-amino-PGA, its rapid effects, and the fact that its actions are not readily prevented by PGA, has raised the question whether it is a true folic acid antagonist. However, the sites of its primary actions are confined to the bone marrow and mucosa of the intestinal tract in guinea pigs<sup>58</sup>, mice<sup>85</sup>, rats, and dogs<sup>69,88</sup>. Changes in bone marrow are consistent with the effects of folic acid deficiency. Mice exhibit depletion of nucleated erythroid elements<sup>85</sup> and rats, guinea pigs, and dogs show a marked reduction of all hematopoietic elements. Moreover, in dogs, erythropoiesis becomes partly megaloblastic, a finding which has been observed with regularity in patients undergoing treatment with 4-amino-PGA and its congeners<sup>3,87</sup>. Damage to bone marrow and megaloblastic erythropoiesis and also destruction of the intestinal epithelium are marked within 24 hours after the administration of lethal doses of 4-amino-PGA. Similar changes are observed following the use of less

potent analogs of 4-amino-PGA, namely 4-amino-N<sub>10</sub>-methyl-pteroylglutamic acid and 4-amino pteroylaspartic acid<sup>22,70,26a</sup>.

On the basis of the evidence just summarized it has been concluded that the administration of 4-amino congeners of PGA in effective doses induces signs of PGA-deficiency<sup>70</sup>. The extreme nature of the lesions noted and the rapidity of their onset warrant the use of the term, "absolute deficiency," in descriptions of the syndrome reproduced by these agents. The agents may quickly deprive dependent cells of the vitamin resulting in metabolic derangement and, in turn, necrosis.

EFFECT OF PGA AND CONJUGATES ON EXPERIMENTAL TUMORS. Leuchtenberger *et al.* reported in 1945 complete regression of 38 of 89 spontaneous breast cancers in 3 different strains of mice treated with daily injections of 5 micrograms of an *L. casei* factor<sup>49,52</sup>. The percentage of spontaneous regression was only 1% as compared with 43% of their injected animals. The same group of workers reported inhibition of growth of transplanted Sarcoma 180 with folic acid concentrates and fermentation *L. casei* factor (pteroyl-tri-glutamic acid, teropterin, PTGA) in short term experiments<sup>50,51</sup>.

These results could not be confirmed by subsequent investigations<sup>72,80,97</sup>; neither did PTGA nor PGA, when injected into mice inoculated with leukemic cells inhibit the development of the leukemia or prolong the life of experimental animals<sup>77</sup>. Moreover, treatment with 100 mg. per kg. per day of PGA failed to inhibit the growth of sarcoma T241 in mice<sup>80a</sup>. Doses of 50 mg. per kg. per day had no inhibitory effect on mammary adenocarcinoma (E0771), Harding-Passey melanoma, Wagner osteogenic sarcoma, and Patterson lymphosarcoma in mice, nor on sarcoma 39 and Flexner-Jobling carcinoma in rats<sup>80a</sup>. Furthermore, no

growth inhibiting effect of PTGA was noted on Sarcoma 180 or the spindle cell tumor Ma387 growing on the chorioallantoic membrane of the chick embryo<sup>77</sup>.

**EFFECT OF PGA AND CONJUGATES ON HUMAN TUMORS.** Farber and coworkers<sup>19</sup> studied the effect of pteroyl-diglutamic acid (diopterin) and PTGA on 90 cases of advanced carcinoma and sarcoma in man. The tumors included gliomata of brain, sarcoma of bone, acute leukemia, lymphosarcoma, Hodgkin's disease, seminoma, and carcinoma of tongue, pharynx, esophagus, stomach, colon, rectum, kidney, bladder, prostate, cervix uteri, ovary, and gall bladder. No curative effect was noted after an average period of treatment of 5 weeks with average daily doses of 20 mg. of either drug. Only a few temporary regressions in size of subcutaneous nodules or of large metastases were seen. Many patients improved in morale and felt better from being given a new drug and much attention. In some cases, however, there was also a diminution in pain and in requirement for sedation or analgesis.

A later report<sup>56</sup> described the effect of PTGA on 7 cases with chronic lymphoid leukemia, 2 with chronic myeloid leukemia, 2 with multiple myeloma, and 2 with acute lymphoblastic leukemia. The patients were treated for periods of 4 to 10 weeks with doses ranging up to 200 mg. per day. In the cases of acute lymphoid leukemia PTGA appeared to convert the acute course into a chronic one. In the other cases there was no effect. Further studies<sup>48</sup> of 20 cases of advanced widespread cancers treated with PTGA for periods of 1 to 3 months with daily intramuscular injections of 50 mg. failed to reveal objective evidence of tumor regression. Nevertheless, dramatic clinical improvements were described. Labora-

tory studies showed a decrease of abnormally elevated alkaline or acid phosphatase but no changes in hematology. All patients exhibited a sense of well being and often the requirement for opiates was decreased.

Another group<sup>84</sup> treated 35 patients with advanced carcinoma. Twenty to 50 mg. of PTGA were given intramuscularly twice daily for periods of 2 weeks to 12 months. In 34 cases no change in the natural course of the disease was noted. In one case, however, a complete regression of metastatic nodules of a breast cancer in the lung followed 3 months of daily doses of 40 mg. A further case of regression in advanced metastatic breast carcinoma was reported in a patient receiving PTGA but previously treated with oophorectomy and testosterone<sup>44,45</sup>.

Since some of the findings reported above created widespread interest and expectation, the Council on Pharmacy and Chemistry of the American Medical Association<sup>2</sup> deemed it necessary to explore the current status of PTGA and diopterin in the treatment of human cancer. On the basis of results submitted to the Council of 154 cases treated with PTGA and 121 cases treated with diopterin, it was concluded that the agents had no specific anti-carcinogenic effects. This conclusion is supported by experiences mentioned above with experimental tumors in which the majority of investigators failed to find tumor-inhibiting action by either PGA or its conjugates. Indeed it would be paradoxical to find folic acid in free or conjugated form acting as a growth-inhibitor.

**EFFECT OF PGA DEFICIENCY AND ANTAGONISTS ON EXPERIMENTAL TUMORS.** As mentioned previously the role of folic acid for the maintenance of proliferating tissues stimulated studies of the influence of deficiencies on

the growth of neoplastic tissues. Working with a single strain of New Hampshire red chickens susceptible to Newcastle disease, Little and coworkers<sup>33,34</sup> showed that the growth of Rous sarcoma could be controlled by regulating the amount of PGA in the diet of chicks. The authors reported the failure of Rous sarcoma to "take" or develop in one day old chicks maintained on PGA-deficient diets for 21 days after inoculation with the tumor; controls died with tumors within 16 days after inoculation. Small amounts of folic acid added to the diet stimulated tumor growth. However, in 6-week old birds kept on the folic acid deficient diet Rous sarcoma "took" in 60%. Subsequent therapeutic studies with 4-amino-PGA and related antagonists were carried out on baby chicks, 1 and 2 days old, maintained on a diet permitting tumor growth<sup>33,55</sup>. In the chicks tumor development was inhibited in a high percentage of cases. The compounds were found to be toxic and, while preventing the development of tumors, killed the chicks with signs of folic acid deficiency. In 4- to 9-week old chicks with established Rous sarcoma a tumor-inhibiting effect of 4-amino-PGA and 4-amino-pteroyl aspartic acid (4-amino-PAA) was also seen. In eggs, however, 4-amino-PGA, in doses fatal to the embryo within 4 to 7 days, failed to inhibit the growth of Rous sarcoma on the chorioallantoic membrane<sup>42a</sup>.

The effect of 4-amino folic acids was studied on mouse tumors, Sarcoma 180 and Ma387, growing on the chorioallantoic membrane of embryonated eggs. The tumors were well established on the 12th day when the yolk sacs were injected with the compounds. Sarcoma 180 showed severe damage with cytoplasmic vacuolation and widespread necrosis. Sarcoma Ma387 showed only minor damage. Both tumors, however, were still viable on

bioassay in susceptible mice. The doses necessary to produce lesions in the tumors were lethal to chick embryos<sup>42a,77</sup>.

Extensive studies with 4-amino-PGA and related antagonists were carried out in mice (AKM) with different strains of leukemia<sup>8,77</sup>. The survival time of treated mice after inoculation with leukemic cells was compared with that of controls as a measure of tumor inhibition. The 4-amino compounds were given first 48 hours after the leukemic cells were injected. Treatment was continued 3 times weekly for 10 doses. It prolonged survival time in varying degrees for different strains but produced no cures. Furthermore, mice with an established leukemia injected with supralethal doses and sacrificed 2 and 48 hours later gave positive bioassays for leukemic cells.

Of great interest were findings of the effect of 4-amino-PGA and related compounds on a series of mouse and rat tumors<sup>60,72,77</sup>. Susceptible mice were inoculated with Sarcoma 180 and after 24 hours treatment was initiated with varying doses. During treatment with effective doses tumor growth was inhibited but was resumed as soon as therapy ceased. When the administration of antifolic compounds was delayed for more than 24 hours after tumor implantation, the inhibitory effect of treatment became progressively weaker and was hardly noticeable after 7 days delay. The materials were found to be rather toxic to mice and the range between tumor dose and lethal dose was narrow. Doses effective against tumor growth also depleted normal erythropoiesis in bone marrow<sup>85</sup>. Of the agents tried, 4-amino-N<sub>10</sub>-methyl-PGA provided the most favorable range of therapeutic activity.

Further studies with 6 other mouse and 2 rat tumors using a similar technique, but giving the tumors in rats a 6

day start, were very illuminating<sup>77,80b</sup>. The investigators found marked inhibition of the Patterson lymphosarcoma in mice and of the reticulum cell sarcoma, R39, in rats. Sarcoma R39 appeared to be so sensitive that on several occasions bioassays in rats were negative with tumor material from treated animals. These experiments provided a spectrum of reaction of experimental tumors according to their susceptibility to the antifolic compounds. The effective tumor doses in the rats were quite toxic; many died with depletion of the marrow and intestinal lesions. The mammary adenocarcinoma, E0771, and the Harding-Passey melanoma in mice showed only a slight inhibition. The Wagner osteogenic sarcoma in mice characterized by a high alkaline phosphatase as well as the Flexner-Jobling carcinoma in rats showed no inhibition whatsoever.

According to the above findings the 4-amino-folic acids prevent the development of Rous sarcoma in New Hampshire Red baby chicks and in a few cases cure the rat sarcoma, R39. The effect on a few other susceptible tumors is only growth-inhibition but never curative and to obtain this action the compounds have to be given shortly after tumor implantation. The results clearly indicate that a great variety of susceptible and resistant tumors exists.

**EFFECT OF 4-AMINO-PGA AND RELATED ANTAGONISTS IN HUMAN CANCER.** The early reports of the use of folic acid antagonists in the treatment of human leukemia created much interest. After it had been observed that 3 cases of chronic myeloid leukemia rapidly relapsed under treatment with PGA and improved on withdrawal of the vitamin, a crude antagonist, "X-methyl folic acid," was employed in one further case<sup>33</sup>. A remission resulted after 100 days of treatment. On withdrawal

of the antagonist the leukemia relapsed. A second remission had begun following renewed treatment with the antagonist when the patient died.

About the same time investigations were in progress employing the first of the series of 4-amino-analogs, namely, 4-amino-PGA or aminopterin. Later members of the series include 4-amino-N<sub>10</sub>-methyl-PGA or amethopterin and 4-amino-PAA or amino-an-fol. Farber, Diamond, *et al.*, were the first to report preliminary studies with aminopterin in 16 children with acute leukemia<sup>20</sup>. Various degrees of temporary improvement occurred during therapy in 10 cases. Details of laboratory studies and clinical findings were given of 5 cases. Six failed to respond and 4 of these were dead at the time of reporting. Spleen, liver and lymph nodes decreased in size and a marked effect on the leukemic bone marrow with decrease of immature cells in the peripheral blood was noted in responsive cases. Hemoglobin and platelets tended to return to normal. Studies on bone marrow showed changes varying from a decrease to a disappearance of leukemic cells. A wide range of general hypoplasia of the marrow with erythrocyte precursors and megakaryoblasts was seen. Further toxic manifestations of the drug such as stomatitis with ulceration occurred, and crude liver as well as PGA and conjugates were given to forestall them. Blood transfusions and antibiotics were also given as supporting therapy whenever necessary.

In a later paper Farber<sup>21</sup> reported remission in cases of Hodgkin's disease, lymphosarcoma, and neuroblastoma, exact details of which have not yet been published. Also reported were results of 60 children with acute leukemia treated with aminopterin, amethopterin, or amino-an-fol. Clinical and hematological improvement were claimed in about 50% of these

cases, which have not yet been described in detail. The effective daily doses used were 0.5 to 1.0 mg. for aminopterin, 3 to 5 mg. for amethopterin, and 25 to 50 mg. for amino-anfol. In this group stomatitis, ulceration of mouth and tongue, pharyngitis, atrophic changes in the intestinal epithelium, diarrhea and intestinal hemorrhage, and depletion of the marrow leading to aplasia were noted. Efforts to counteract these effects with liver extract, vitamin B-complex and folic acid, were only partially successful. Suspension of administration of antagonists for 4 to 7 days appeared to be more effective.

Farber introduced an arbitrary minimum of 3 weeks of life of an acute leukemia while under treatment with antifolic compounds as basis for admission of the case to his statistics. During this period the patients most severely ill will have died or the antifolic therapy given will have had an opportunity to affect the disease. This arbitrary selection might explain in part the high proportion of remissions claimed for antifolic therapy. The remissions reported were temporary in all instances though 2 children were alive after about 2 years.

Subsequent investigators, using approximately the same doses of 4-amino-PGA and its analogs in the treatment of leukemia and cancer, encountered often the toxic symptoms described by Farber. Attempts to prevent or treat these lesions with liver extract or folic acid failed and treatment had to be interrupted or abandoned for this reason. Furthermore, no definite pattern of treatment with the 4-amino-folic acids has yet emerged. Treatment is adjusted to the individual tolerance, and requirement varies from case to case. Some investigators have treated until tumor remissions occurred and then continued with a maintenance therapy. Others have

given several separate courses of treatment with intervals when severe marrow changes or tumor remissions occurred.

Additional studies by other workers using similar doses of the 4-amino-folic acid antagonists in the treatment of acute leukemia of childhood revealed further information. Guest<sup>31</sup> had the best results with 7 remissions in 10 consecutive cases. Other authors reported lower incidences of remissions. Meyer<sup>57</sup> saw 4 remissions in 18 cases, Burchenal<sup>9</sup>, 3 in 19 cases, Pierce<sup>71</sup>, 5 in 9 cases, Stickney<sup>76</sup>, a few in 18 cases, and Kracke<sup>46</sup>, slight improvements in 14 of 29 cases. But Neligh *et al.*<sup>61</sup> saw no effect on the clinical course.

In adults with acute leukemia Meyer<sup>57</sup> saw 3 temporary remissions in 20 cases, Dameshek<sup>13</sup>, 9 in 31 cases, Burchenal *et al.*<sup>9</sup>, 2 in 12 cases, and other workers<sup>39</sup>, only occasional improvement.

According to the figures at hand, a total of about 250 cases of acute leukemia in man have been treated with the 4-amino-folic acids with temporary remissions in about 30%. The remissions typically lasted from several weeks to a few months. In some instances several remissions were observed in the same case; but no cure was claimed by any investigator.

In chronic lymphoid leukemia a decrease in immature lymphoblasts and an occasional slight decrease in the size of enlarged lymph nodes but no real remissions were noted<sup>3,9,57,61</sup>. In chronic myeloid leukemia a decrease in total leukocyte count and decrease of the primitive elements with an increase of the more mature forms and a transitory slight decrease of enlarged spleens were noted. However, no remissions occurred comparable to the ones seen in cases of acute leukemia. The erythropoiesis showed in both forms of chronic leukemia marked

depletion and became partly megaloblastic<sup>3,87</sup>.

Other workers<sup>9,84</sup> studied the effects of the 4-amino-folic acids in 40 human cancers. In adults they observed regression of metastasis of 2 cases of breast carcinoma and decrease of the size of a seminoma. In children<sup>9</sup> two cases of lymphosarcoma and 1 case of reticulum cell sarcoma showed temporary remissions. But other cases of lymphosarcoma, Hodgkin's disease, mycosis fungoides, multiple myeloma, neuroblastoma, osteogenic sarcoma, Ewing's sarcoma, cancer of the lung, bladder, stomach, female breast, ovary, sarcoma of the jaw and melanocarcinoma failed to respond.

From the above it is evident that the 4-amino-folic-acid antagonists have a definite action on erythropoiesis, myelopoiesis, and lymphopoiesis in man. The best therapeutic effects so far obtained in cancer of man are repeated temporary remissions of acute leukemia in children and adults.

**Comment.** The evaluation of the effect of the 4-amino-folic acids on the acute leukemias in man is difficult. Unlike the situation in animal experiments with controls and repeatable, well-defined conditions, the diagnosis as well as the course of the disease is variable. According to Diamond (quoted from Farber<sup>21</sup>) in children with acute leukemia spontaneous remissions occur in 10% of all cases. Spontaneous remissions in adults have also been described with an emphatic warning not to forget this fact<sup>37,38</sup>. Furthermore, the diagnosis of acute leukemia is based on the time of death

and sometimes cases diagnosed as acute have become subacute or chronic. The increased care of patients with antibiotics, blood transfusions, and hemostatics and the intense study of the cases under treatment introduce factors not included in previous statistics. However this may be, it is the impression of some investigators that the compounds have a definite effect on the acute leukemic process as reflected in a remission rate never seen before.

One must look forward to future research to explain why only a fraction of the acute leukemias respond to treatment and chronic cases respond so rarely; why in some cases relapses are seen under maintenance therapy with the 4-amino-folic acids; and why in other cases remissions occur following therapeutic attempts when liver and folic acid are given to palliate toxic manifestations.

Experimental work in chickens measuring folic acid requirements of different tissues is of great interest in this connection<sup>7,11,27,63,66</sup>. It has been shown in birds that general growth, growth of feathers, pigmentation, erythropoiesis, and myelopoiesis can be selectively inhibited by varying grades of folic acid deprivation. Such results indicate that growing tissues of the normal organism vary significantly in their needs for folic acid. This can be expected to hold for neoplastic tissues. These experiments might be an indicator for future work to measure the folic acid requirements of tumor cells and for tumor growth and thus to explain varying response of neoplastic tissues to folic acid antagonists.

#### ADDENDUM

Since writing this review, additional information has been received by personal communication. Silverman found regression of leukemic skeletal lesions and the occurrence of heavy transverse bands of increased density at the ends of shafts of long bones in 7 children treated with aminopterin (to be presented before the Society for Pediatric Research, Atlantic City, June 1949). L. Meyer<sup>57</sup> augmented his observations with 8 patients with acute leukemia treated with amino-an-fol without apparent effect. C. H. Smith treated with aminopterin 10 children who had acute leukemia. He observed reductions of blast forms in the marrow in some instances and, in one child, a transitory increase in normoblasts but no true remission.



M. Wintrobe treated 10 patients with acute leukemia with aminopterin and noted a distinct remission in one adult lasting for about 6 months. Two children at present under treatment are doing reasonably well.

J. H. Dale's statistics of the course of acute leukemia in children (J. Radiol., 1949, in press) are of special interest and may serve to assess the effectiveness of chemotherapeutic procedures on the basis of time of survival. Of 72 cases of leukemia in children observed during the period from September 1932 to June 1948, 39 had a complete follow-up. Thirty-six of the cases exhibited clinical manifestations of "acute" leukemia and showed a predominance of blast forms. Twenty-seven (75%) of the 38 cases died within 6 months of onset of the disease, 8 cases (22%) died between 6 months and one year, and one case died after 14 months. These results illustrate the variable course of "acute" leukemia. An even higher percentage might have been expected to survive for longer than 6 months had antibiotics been available during the whole period of the recorded observations. It is against the background of the natural course of the disease and of effects of supportive therapy in the form of blood transfusions and antibiotics that therapeutic claims have to be evaluated.

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# PHYSIOLOGY

PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF FEBRUARY 15, 1949

**Blood Temperature in the Heart and Blood Vessels of the Dog.** STEVEN M. HORVATH, M.S., Ph.D., E. L. FOLTZ, M.D., A. RUBIN, M.D., and B. K. HUTT, P. T. (Dept. of Physical Medicine, Graduate School of Medicine, and the Dept. of Pharmacology, School of Medicine, Univ. of Penna.). Temperatures of the blood, tissues, skin and rectum in anesthetized dogs have been determined. Courmand type catheters with thermocouples at the tip were placed roentgenoscopically in the coronary sinus and the right ventricle or pulmonary artery. These catheters were also used to measure temperature in other areas of the body. Smaller catheters were similarly inserted into the femoral artery and vein. The emf developed by the thermocouple was measured with a type K-2 Leeds and Northrup potentiometer.

The vascular temperatures obtained indicate clearly that the concept of a uniform body temperature is erroneous. The temperature varies widely and is dependent on activity of the organs and the environmental temperature. Since morphine-nembutal anesthesia has a tendency to lower body temperature, it was possible to study the temperature gradients at different rectal temperatures. The following table presents some of the mean temperatures and gradients obtained in 19 experiments on 11 animals.

The work of the heart was altered with intravenous injections of epinephrine, aminophylline and methedrine and with inhalations of amyl nitrite. The temperature of the blood in the right heart and coronary sinus during

the action of drugs was determined. These data were discussed in relation to the effect of these drugs on cardiac work and cardiac efficiency.

Location of Catheter	°F.
Rt. Ventricle	98.7
Pulmonary Artery	98.7
Coronary Sinus	98.9
Femoral Artery	98.3
Femoral Vein	96.6
Muscle, Thigh	97.6
Subcutaneous, Thigh	96.5
Skin, Thigh	92.1
Rectum	99.1

**The Effect of Intravenous Aminophylline upon Cardiac Oxygen Supply and Demand.** E. L. FOLTZ, M.D., A. RUBIN, M.D., and W. A. STEIGER, M.D. (Dept. of Pharmacology, Univ. of Penna., and Division of Cardiology, Philadelphia General Hosp.). Changes in the coronary arteriovenous oxygen difference were studied in 14 normal, intact dogs under morphine-nembutal anesthesia. Arterial blood was obtained by femoral artery puncture while coronary venous blood was sampled from the coronary sinus through a catheter which was introduced under fluoroscopic guidance (*Am. J. Physiol.*, 152, 341, 1948). Simultaneous arterial and coronary venous samples were collected before and after the intravenous injection of either saline or aminophylline solution.

Coronary venous oxygen saturation fell during a period from 4 to 8 minutes after injection of aminophylline; the mean values for saturation decreased from 30.2% to 17.7%, and the unsaturation (Cor. A-V difference) rose from 62.1% to 74.1%. Compared with data of saline control experiments, the dif-

ferences are significant. No measurable change was noted in mean arterial blood pressure; mean pulse rate increased from 145 to 165 beats per minute. Electrocardiographic record revealed no significant change in pattern as a result of catheterization, experimental procedures, or drug injections.

Previous studies have demonstrated that aminophylline dilates the coronary vessels but also stimulates the heart to contract more vigorously with resulting increases in cardiac output and cardiac work; the observed changes in coronary venous oxygen saturation indicate that the stimulating effect of aminophylline increases cardiac oxygen consumption more than the coronary vasodilating action augments coronary flow and the delivery of oxygen. The result is the production or intensification of myocardial anoxia.

**Inhibition of the Knee Jerk from Tendon Spindles of Crureus.** G. P. MCCOUCH, M.D., I. D. DEERING, M.S., W. B. STEWART, M.D., and W. W. CHAMBERS, Ph.D (Depts. of Physiology and Anatomy, Univ. of Penna.), In decerebrate cats the tension of quadriceps and the action potential of rectus and crureus were isometrically recorded. The knee jerk was elicited by a mechanical tapper, which stretched the muscle by raising the lever shank. Conditioning volleys, not significantly above threshold for contraction, were delivered through bare needles of which one passed through the patellar ligament, the other transversely through vastocrureus a few millimeters proximal to the tendon of crureus.

Inhibition curves may be preceded by facilitation at intervals between conditioning and test stimuli up to 2 m. sec. This is followed by a descending limb, which reaches maximal depth within 8 or 9 m. sec. Total duration of inhibition is variable, being greater with more proximal positions of the muscle

electrode, which involve more receptors, than with distal positions which engage fewer end organs. It ranges from 20 to 100 m. sec. With 4 electrodes, one in the patellar ligament and 3 in crureus approximately 10, 21, and 29 mm. from the distal end of the muscle, curves were run conditioning from each adjacent pair. Inhibition was deep from the distal, slight from the middle, and virtually absent from the proximal pair.

Two factors may be postulated to account for the shape of the curve. The first is facilitation from the inevitable involvement of muscle spindles. The second results from the multisynaptic character of the inhibitory arc and its consequent afterdischarge.

**Intermediary Metabolism of Phenylalanine Labeled with C<sup>14</sup>.** BERNARD SCHEPARTZ, Ph.D.,\* and SAMUEL GURIN, Ph.D. (Dept. Physiol. Chem., Univ. of Penna.). Administration of DL-phenylalanine (labeled in the carboxyl and alpha positions) to phlorhizinized rats results in the appearance of C<sup>14</sup> in the urinary ketone bodies as well as in the respiratory CO<sub>2</sub>. Upon incubation of this type of phenylalanine with liver slices, acetoacetate labeled solely in the carboxyl group is obtained.

When ring-labeled phenylalanine (carbons 1, 3, 5) is administered to phlorhizinized rats, C<sup>14</sup> appears in the respiratory CO<sub>2</sub> as well as in the acetone moiety of the urinary acetoacetate. Incubation of ring-labeled phenylalanine with liver slices produces acetoacetate labeled chiefly in the terminal methyl group.

The aromatic ring of phenylalanine readily undergoes cleavage in the course of metabolism, the immediate precursor of acetoacetate being a four-carbon unit derived from the ring and side-chain. Apparently no two-carbon units are involved in this pathway.

It is apparent that the alpha carbon

books will culminate Dr. Friedman's protracted efforts to collect all that is known and some things that are unknown about this interesting and widely prevalent parasitosis.

The first volume unites in revised form 2 of the author's previously published works ("Scabies—Civil and Military" (1941) and "Biology of *Acarus Scabei*" (1942)). It deals with scabies from the earliest times to the beginning of America's participation as an active belligerent in World War II. Volume 2 will contain the advances made from the beginning of World War II until the end of 1947. Volume 3 will be devoted to the history of scabies, and Volume 4 will contain chiefly translations of certain classical contributions to our knowledge of scabies.

Written by one of the world's foremost authorities on scabies, this volume meets the reviewer's most critical expectations. Nothing of importance has been omitted. It is beautifully illustrated and well written. It has appeal both for the medical historian and the clinician.

H. B.

**HANDBOOK OF DISEASES OF THE SKIN.** By RICHARD L. SUTTON, M.D., and RICHARD L. SUTTON, JR., M.D., Univ. of Kansas Medical School. Pp. 749; 1057 ills. St. Louis: C. V. Mosby, 1949. Price, \$12.50.

The Suttons have achieved brevity and practicality in their production of a new text for medical students, practitioners and specialists in dermatology. Although this Handbook is a small volume, it contains more useful, well presented, well documented and well illustrated material than many texts twice its size. It is, however, not a mere catalog of the views of various contributors to the subject but contains many original personal views, especially the technic in contact dermatitis of relieving the patient by elimination of all possible causes, then identifying the actual cause by systematic increment of the patient's chemical environment. Acne vulgaris and urticaria are also treated by the authors' special techniques. The 1057 illustrations are well chosen; especially notable are those dealing with the normal adult and fetal skin. The text itself is well written and with adequate detail. Some sections are superbly handled. It is presented in a logical order and with good correlation of the eutaneous manifestations with general medicine and biology. There are surprisingly few typographical errors in this book.

The difficult matter of references to the literature is handled in novel fashion by placing references parenthetically as near the

material cited as possible. This is somewhat disturbing to the average reader, but is more so to the experienced worker, because as a space-saving device the authors have still further abbreviated the already abbreviated names of the medical journals referred to. The reviewer hopes that, if possible, some less distracting method will be considered for future editions.

The Suttons have produced another creditable aid to the understanding of dermatology. It deserves wide acceptance.

H. B.

**BLOOD TRANSFUSION.** By ELMER L. DEGOWIN, M.D., Assoc. Prof. of Internal Medicine, ROBERT C. HARDIN, M.D., Ass't Prof. of Internal Medicine, State Univ. of Iowa, and JOHN B. ALSEVER, M.D., Senior Surgeon U. S. Pub. Health Service. Pp. 587; 200 ills. Philadelphia: W. B. Saunders, 1949. Price, \$9.00.

ALTHOUGH good books dealing with the problems of blood transfusion are available, a new one of this calibre is welcome. Its authors have had extensive experience in the field of transfusion therapy and have made, individually and as a group, original contributions of considerable importance. Their book is clearly and simply written. All important problems which confront the personnel of a transfusion service are discussed. The chapter on laboratory procedures is of unusual value because of its simplicity, detail, and ingenious illustrations. This book is highly recommended to all who are interested in the transfusion of blood and blood derivatives, from technicians to experts.

C. K.

**SURGERY OF THE EYE.** By MEYER WIENER, M.D., Emeritus Prof. of Clinical Ophthalmology, Washington Univ. School of Medicine, 2d ed. Pp. 426; 425 ills. New York: Grune & Stratton, 1949. Price, \$12.00.

This 2d edition has been badly needed. It possesses the advantages of being reasonably short and the material is presented in a lucid and concise manner. The illustrations are up to the standard set in the 1st edition.

Those procedures that have been useful to the author are described with the variations in technique which he employs. Some of the newer operations, such as the Burch implant and evisceration and goniotomy are included. Procedures still regarded as experimental in nature, such as the various types of exposed implant following enucleation, are omitted. The author describes his punch technique for keratoplasty which this reviewer believes

might be dangerous, due to the danger of iris prolapse.

H. S.

ATLAS OF PERIPHERAL NERVE INJURIES. By WILLIAM R. LYONS, Ph.D., Assoc. Prof. of Anatomy, Univ. of California Medical School, and BARNES WOODHALL, M.D., Prof. of Neurosurgery, Duke Medical School. Pp. 339; 135 ills., 15 in color. Phila.: W. B. Saunders, 1949. Price, \$16.00.

UPON 135 large size plates, 15 of them in color, this book furnishes complete documentary evidence of the pathological changes in proximal and distal stumps of severed nerves, of nerve lesions in continuity as found in resected parts of the injured nerve, of the consequence of various types of sutures which proved unsatisfactory and had to be removed, and of several kinds of grafts. Each chapter is preceded by a clear summary of the findings, beginning with the structure of the normal nerve. The microphotographs and the accompanying legends are excellent and show distinctly the various sheaths of the nerve and their cells in normal and pathological conditions. Instructive photographs of skin scars, Roentgen-ray pictures of fractures and bone deformities, examples of the gross appearance of nerves and their operative repair and of the pathological specimen and the microscopic changes under low and high power, together with the comprehensive clinical and pathological description, give a vivid picture of the processes at different time intervals following nerve injuries.

The book is indispensable for the neurosurgeon and the neuropathologist, for the general pathologist who is concerned with nerve injuries in industry or war, and for most neurologists. It will remain a standard book for years to come.

F. L.

#### NEW BOOKS

*Atlas of Neuropathology.* By WILLIAM BLACKWOOD, Ass't Pathologist, Nat. Hosp., Queen's Square, London, T. C. DODDS, Lecturer, Society of Radiographers, Scottish Branch, and J. C. SOMMERVILLE, Univ. of Edinburgh. Pp. 199; 262 ills. Balt.: Williams & Wilkins, 1949. Price, \$9.00.

This small atlas should prove of considerable value to those whose work brings them into occasional contact with neuropathology. It is brief and selects only the highlights of each lesion presented, and for that reason might be of less value to the full-time neuropathologist. The range of subjects covered is broad, but the salient features of each subject are clearly brought out, no space is wasted on ramifications which are not strictly within the

field of neuropathology. The illustrations are well chosen and technically excellent. The reviewer recommends the book highly. A. R.

*Clinical Orthoptics.* By MARY EVERIST KRAMER. Edited by ERNEST A. W. SHEPARD, M.D., Prof. of Ophthalmology, George Washington Univ. School of Medicine, and LOUISA WELLS-KRAMER. Pp. 475, 147 ills. St. Louis: C. V. Mosby, 1949. Price, \$8.00.

This is one of the first texts on orthoptics to come from this country, the previous standard texts having all been written in England. The work covers the various phases of knowledge which an orthoptic technician should acquire before presenting herself to the American Board of Orthoptics for examination. The anatomy and physiology of the eye are given adequate consideration. The main portion of the book deals with the treatment of the various forms of strabismus by means of orthoptics.

The book is highly recommended for all those who are interested in the subject of strabismus. F. A.

*Child Health.* Edited by ALAN MONCRIEFF, Nuffield Professor of Child Health, University of London, and WILLIAM A. R. THOMSON. Pp. 254. London: Eyre and Spottiswoode, 1947. Price, 14s.

This "Practitioner Handbook" is an expository presentation, with chapters contributed by many authorities, describing for general practitioners the new English system of the numerous organized child health services. There are chapters on Child Welfare Centers, School Health Services, Day Nurseries, Schools for Crippled Children, and so forth. There are also several chapters on nutrition, feeding, and prevention of certain diseases. The American pediatrician will find much information of usefulness in these pages, despite the fact that the text is slanted to the problems of another country. I. W.

*Facts About Nursing, 1948.* By AMERICAN NURSES' ASSOCIATION. Pp. 106. New York. A. N. A., 1790 Broadway, 1949. Price, 35c.

"The first authoritative survey since the war among U. S. nurses."

*Diabetic Menus, Meals and Recipes.* By BETTY M. WEST. Introduction by RUSSEL F. RYPINS, M.D. Pp. 254. New York: Doubleday, 1949. Price, \$2.95.

*The Psychoanalytic Reader.* Edited by ROBERT FLIESS, M. D. Vol. 1. Pp. 392. New York: International Universities Press, 1949. Price, \$7.50.

"The contributions united here have been gathered by scanning the complete literature of the field, from the oldest Viennese *Jahrbuch für Psychoanalyse*, founded in 1909, to the British and American psychoanalytic periodicals of today . . . What appears most profitable of this literature will be published in the Reader's several volumes, of which the present one is the first . . ."

*Social Medicine, Its Derivations and Objectives.* Edited by IAGO GALDSTON, M. D. The New York Academy of Medicine Institute on Social Medicine. Pp. 294. New

York. Commonwealth Fund, 1949. Price, \$2.75.

In this study of the origins and aims of Social Medicine, the contributions of the 26 well known participants are arranged in 7 groups. The first 2, of a more general nature, are on the relation of medicine to society and the relation of social medicine to clinical and preventive medicine. The other 5 treat special aspects such as the place in social medicine of epidemiology, nutrition, psychiatry. This is a worthy and valuable statement of current thought on a highly important subject that has not hitherto received sufficient attention by the medical profession in this country. E. K. \*

*Medical Clinics of North America.* Chicago Number. *Diseases of the Skin.* Pp. 292, 135 ills. Phila.: W. B. Saunders, January, 1949. Price, \$15.00 a year.

THE wide coverage of this well organized and composed symposium is indicated by a list of the subjects discussed, which include: neurodermatitis, dermatomyositis, sarcoidosis, scleroderma, disseminated lupus erythematosus, changes in the nail from the use of "hose coats," tumors of the skin, exfoliative dermatitis, herpes, pemphigus, cutaneous allergy, eruptions due to food, cutaneous tuberculosis of the Negro, dermatological therapy and dermatopathology. H. B.

*Cancer of the Esophagus and Gastric Cardia* Edited by GEORGE T. PACK, M.D., Clinical Prof. of Surgery, New York Medical College. Pp. 192; 65 ills. St. Louis: C. V. Mosby, 1949. Price, \$5.00.

THE 11 papers of this specially bound volume of the June 1948 issue of "Surgery" are written by men outstanding in the recent developments in this field. The book affords an excellent summary of American surgical practice in relation to this disease. J. J.

*Collateral Circulation (Anatomical Aspects).* By DANIEL P. QUIRING, Ph.D., Assoc. Prof. of Biology, Western Reserve Univ. Pp. 142; 61 ills., 46 in color. Phila.: Lea & Febiger, 1949. Price, \$5.00.

THIS compact presentation, by description and diagram, of the major cross connections and side channels of arteries and veins has obvious values for the internist and surgeon as well as the anatomist and physiologist. Five of the 8 chapters deal with the collateral circulation of a given body region, involving such important problems as results of occlusion of cerebral, acoustic, coronary arteries, and others, and with the benefits that may be brought by collateral circulations. Venous collateral circulation with a different set of problems is considered in each section, the book closing with a suggestive illustration of Beck's experimental revascularization of the dog's heart.

THIS correlation by an anatomist of gross structure with clinical problems should find welcome space on many shelves. E. K.

## NEW EDITIONS

*Surgical Technique and Principles of Operative Surgery.* By A. V. PARFUMLO, M.D., F.A.C.S., Assoc. Clinical Prof. of Surgery,

Loyola Univ. 4th ed. Pp. 676, 997 ills. Phila.: Lea & Febiger, 1949. Price, \$15.00.

THIS 4th edition is the 1st to be published by Lea & Febiger. The book is well illustrated and well printed. A consistent editorial plan has not been followed in regard to references and questionnaires: certain chapters have good bibliographies following them, some have none, certain chapters are followed by rather elementary questionnaires, some are not. The reason for this lack of uniform policy is not clear.

While the Reviewer does not agree with a number of procedures advocated by the authors and thinks that if physiologic considerations are discussed at all they should be given greater attention, he would recommend this book to the young surgeon for a review of operative procedure. I. R.

*The Mentally Ill in America.* By ALBERT DEUTSCH. 2d ed. Pp. 555; 8 ills. New York: Columbia Univ. Press, 1949. Price, \$5.50.

THE 2d edition of this worth while book includes additions and revisions, such as a new chapter entitled "Psychiatry in World War II" and a completely revised chapter on modern trends in institutional care and treatment. The book is directed toward the general reader as well as the physician. W. P.

*Child Psychiatry.* By LEO KANNER, M.D., Assoc. Prof. of Psychiatry and Pediatrics, Johns Hopkins Univ. 2d ed. Pp. 752. Springfield, Ill.: Charles C Thomas, 1949. Price, \$8.50.

THIS new edition of a comprehensive and valuable text published 13 years after the appearance of the 1st edition will be welcomed by pediatricians, psychiatrists, and others. Extensive revisions and additions have been made that give greater clarity and depth to the work. W. P.

*Human Embryology and Morphology.* By SIR ARTHUR KEITH. 6th ed. Pp. 690; 578 ills. Balt.: Williams & Wilkins, 1948. Price, \$10.00.

THIS new edition presents numerous improvements. Chapters on the development of the urogenital system and limb evolution have been added. There are numerous new illustrations. Recent factual material and references are included. The chapter on experimental embryology seems inadequate, considering how profitable has been this field of investigation. The occasional use of strained analogies often confuse the understanding of the facts presented. This edition is an excellent reference text for morphological changes occurring during embryogenesis. I. Z.

*Manual of Clinical Laboratory Methods.* By OPAL E. HEPLER, Ph.D., M. D., Assoc. Prof. of Pathology, Northwestern Univ. Medical School. 4th ed. Pp. 387; 36 figs., 8 color plates. Springfield Ill.: Charles C Thomas, 1949. Price, \$8.50.

*The Business Side of Medical Practice.* By THEODORE WIPRUD. 2d ed. Pp. 232; 22 figs. Phila.: W. B. Saunders, 1949. Price, \$3.50.

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## ORIGINAL ARTICLES

### RAPID ATTAINMENT OF THERAPEUTIC PENICILLIN CONCENTRATIONS IN THE CEREBROSPINAL FLUID

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THE complications observed following the intrathecal administration of penicillin<sup>8,14,19,20</sup> justify a re-evaluation of the possibility of attaining therapeutically significant penicillin concentrations in the cerebrospinal fluid following parenteral administration. It is generally stated that the blood-brain barrier hinders the free exchange of penicillin between the plasma and the cerebrospinal fluid but the support for this statement comes from investigations carried out with smaller doses of penicillin than are currently in wide use. It has been suggested that larger doses of penicillin might cause diffusion into the cerebrospinal fluid but few data are available to substantiate this supposition.

Measurable quantities of penicillin have been observed in the cerebrospinal fluid following its parenteral administration. Ten to 25 million units given by continuous intravenous infusion<sup>18</sup> and 100,000 units intra-

muscularly every 3 hours<sup>2</sup> have given rise to comparable penicillin concentrations in the cerebrospinal fluid of those patients in whom diffusion of the antibiotic from plasma to sub-arachnoid space occurred. Neither of these investigations have answered the question of how soon after the initial administration of penicillin the drug is demonstrable in the cerebrospinal fluid. In this paper we present data indicating that penicillin can be found in the cerebrospinal fluid 2 and 3 hours after a single intravenous injection of penicillin.

**Patients studied.** Twenty-one patients suffering from central nervous system syphilis (paresis) were studied. These patients were not selected in any way and apart from their neurological disease were in good or fair general health.

**Method of Study.** Because a review of the literature indicated the likelihood of failure to obtain assayable quantities of penicillin in the cerebrospinal fluid of normal patients un-



less a blood concentration of 10 to 30 units per cc. of plasma was attained for some length of time, commonly used doses of penicillin (20,000 to 50,000 units every 3 hours) were

not employed in this study. A single intramuscular dose of 500,000 units of penicillin will give plasma concentrations above 12 units per cc. for at least 30 minutes<sup>13</sup> and

TABLE I.—PENICILLIN CONCENTRATIONS IN PLASMA AND CEREBROSPINAL FLUID AFTER INTRAVENOUS INJECTION OF 500,000 UNITS WITH AND WITHOUT 3 GM. CARONAMIDE INTRAVENOUSLY.

PATIENT	CARONAMIDE	PENICILLIN CONCENTRATIONS*				
		BLOOD			CSF	
		5 min. (after penicillin)	2 hrs.	3 hrs.	2 hrs. (after penicillin)	3 hrs.
<b>GROUP I</b>						
LR	-	70.90	1.08	.416	.023	.045
NT	-	70.90	4.32	2.160	0	.023
JM	-	X	2.88	.496	.023	.045
AVER. PENICILLIN		70.90	2.78	1.024	.015	.037
<b>GROUP II</b>						
JM	-	23.81	.992	.124	.031	.021
	+	95.23	1.98	.496	.062	.062
RR	-	67.58	.248	.124	.031	.031
	+	184.32	8.61	4.32	.045	.045
JS	-	70.92	1.08	.416	.045	.045
	+	X	5.76	2.16	.090	.045
AJ	-	70.92	1.41	.416	.045	.023
	+	95.23	2.98	.992	.026	.093
WV	-	46.08	.720	.416	0	.023
	+	47.62	1.98	1.15	.016	.031
IJ	-	34.56	X	1.08	.023	.015
	+	63.49	2.11	.992	.031	.031
WW	-	63.49	1.49	.744	.045	.023
	+	63.49	7.94	2.97	.062	.095
SF	-	31.11	.711	.218	.023	0
	+	69.12	2.88	1.08	.015	.023
BC	-	63.49	.992	.218	.045	.045
	+	63.49	5.95	.999	.062	.062
RvL	-	31.74	.496	.186	0	.023
	+	137.52	2.16	1.08	.045	.023
JO	-	46.08	.714	.121	0	0
	+	137.52	1.32	1.08	.023	.023
RM	-	31.71	.992	.248	.023	0
	+	137.52	8.61	2.88	.045	.045
HZ	-	63.49	1.98	1.08	.045	.045
	+	137.52	11.52	5.76	.045	.090
VA	-	31.74	1.19	.496	.090	.045
	+	34.56	5.74	2.50	.135	.135
GG	-	63.40	1.98	.196	.023	.023
	+	69.12	5.74	2.50	.022	.045
AVER. PENICILLIN		49.37	1.10	.430	.031	.026
AVER. PENICILLIN + CARONAMIDE		95.41	5.22	2.08	.050	.056
<b>GROUP III</b>						
DG	+	137.52	2.88	1.08	.023	.023
Tw	+	47.62	1.98	.744	.031	.031
AC	+	92.16	2.88	1.11	.045	.023
AVER. PENICILLIN + CARONAMIDE		92.43	2.58	1.088	.033	.025

\* Penicillin proven by inhibition with penicillinase; penicillin measured in units per cc.

the same dose introduced intravenously will give peak concentrations of between 30 and 70 units per cc. and above 10 units per cc. for 30 minutes. The intravenous route of administration was employed in order to obtain the advantage of a brief but high penicillin plasma concentration immediately after administration that might favor diffusion across the blood-brain barrier. Penicillin in aqueous solution (500,000 units) was given intravenously (injection time being 7 to 15 seconds) and thereafter blood specimens were obtained at 5 minutes, 2 hours and 3 hours. In addition, 2 and 3 hours after therapy with penicillin, lumbar puncture was performed with a 21 gauge needle and the cerebrospinal fluid specimens obtained for penicillin assay. Blood and cerebrospinal fluid specimens were assayed for penicillin by a modified Rammelkamp serial dilution method employing a Group A hemolytic streptococcus as the test organism. Three patients (Table 1, Group I) were studied in the above manner following the administration of 500,000 units of penicillin alone and 3 patients (Table 1, Group III) received the same dose of penicillin and 3 gm. of caronamide intravenously in aqueous solution. An additional 15 patients (Table I, Group II) were investigated twice, once after the intravenous administration of 500,000 units of penicillin alone and again after the intravenous administration of 500,000 units of penicillin together with 3 gm. of caronamide. The same schedule of sampling of the blood and cerebrospinal fluid was followed in the two periods of study. Each patient was his own control and intervals of 7 to 27 days intervened between the two periods of study.

**Results.** The results obtained in this study are presented in Table 1. The administration of 500,000 units of penicillin in aqueous solution resulted in demonstrable concentrations of penicillin in the cerebrospinal fluid at 2 hours in 14 of 18 individuals, and at 3 hours in 15 of 18 persons (Groups I and II). When the same dose of penicillin was administered with 3 gm. of caronamide, penicillin appeared in the cerebrospinal fluid at 2 and 3 hours in all of the 18 patients (Groups II and III). The plasma concentrations resulting from the administration of penicillin were enhanced by caronamide from 2 to 5 times, and the cerebrospinal fluid concentrations

were doubled. The caronamide concentrations observed in the plasma after the intravenous administration of 3 gm. of the drug were adequate to inhibit penicillin excretion by the renal tubules.<sup>3</sup>

The results obtained in the group of 15 patients (Group II) studied as their own controls in both phases of the investigation were statistically analyzed and it was found that the difference in plasma and cerebrospinal fluid penicillin concentrations as a result of the administration of caronamide were highly significant ( $p=0.02-0.05$ ). The difference observed between the 2 and 3 hour determinations of penicillin in the cerebrospinal fluid were not significant either when penicillin alone or penicillin in conjunction with caronamide were administered.

**Discussion.** The complications that have been reported as due to intrathecal injection of penicillin may indeed have been due to the drug, but it seems reasonable to concede the possibility that some of the complications have been due to the disease treated. Furthermore, the use of penicillin less refined than that currently available and the use of unnecessarily large doses may have accounted for some of the results attributed to intrathecal injection of the antibiotic. Nevertheless, if it could be established that penicillin can, with regularity, be demonstrated in the cerebrospinal fluid following parenteral administration, intrathecal administration might be limited to a relatively few patients presenting definite indications for this route of injection.

Any particular concentration of penicillin has little meaning from a therapeutic standpoint unless it is interpreted in terms of both the sensitivity of the organism producing the infection under treatment and the defense

mechanisms of the host in whom the infection is being treated. Wide recognition has been given, however, to a penicillin concentration of 0.03 unit per cc. as being "therapeutically significant" because this amount of the antibiotic "is adequate to sterilize actively growing cultures of almost all strains of gonococcus, Group A hemolytic streptococcus, pneumococcus and most strains of alpha hemolytic streptococcus, about half of the strains of meningococcus, and a somewhat smaller proportion of strains of pathogenic staphylococci".<sup>15</sup>

Penicillin concentrations of this magnitude have been observed in the cerebrospinal fluid of persons suffering from central nervous system syphilis following the administration by continuous intravenous drip of 10 to 25 million units during a 24 hour period, but only when doses of 20 to 25 million units were so administered were these amounts of penicillin demonstrated in all patients.<sup>18</sup> Comparable penicillin concentrations in the cerebrospinal fluid were observed in similar patients following the administration of 100,000 units intramuscularly at intervals of 3 hours,<sup>2</sup> but in only 18 of 23 patients when penicillin alone was given and only 20 of 25 patients when penicillin was given in conjunction with caronamide. Apart from these reports the consensus is that either no penicillin or only a small amount in an occasional patient<sup>7,9,10,12,16</sup> crosses the hematoencephalic barrier of a normal person. There is precedent in the medical literature for regarding paretics as having "normal" barriers between the plasma and cerebrospinal fluid,<sup>11,18</sup> and there is good evidence to believe that the inflamed tissues interposed between plasma and cerebrospinal fluid offer less impediment to the passage of penicillin than those not so involved.<sup>5,11,17</sup>

In view of the greater permeability

of an inflamed hematoencephalic barrier<sup>11</sup> there is every reason to believe that an amount of penicillin in the plasma that will cause diffusion of measurable quantities of drug into the cerebrospinal fluid of normal patients (paretics) will cause diffusion of even greater amounts in patients with meningitis. It should be emphasized, however, that before the results of an investigational study are applied to therapy, the schedule of penicillin therapy employed should offer reasonable assurance that the diffusion of significant quantities of penicillin into the cerebrospinal fluid will occur in all normal individuals. The demonstration of assayable quantities of penicillin in the cerebrospinal fluid of even a few patients following parenteral penicillin is of academic interest but unless it can be shown that significant amounts of penicillin can be observed in 100% of patients so treated, it would be hazardous to rely entirely upon parenterally administered penicillin for the treatment of meningitis.

One hundred thousand units intramuscularly every 3 hours, either alone or given in conjunction with caronamide,<sup>2</sup> failed to fulfill this criterion, and so also have 10 and 15 million units administered by continuous intravenous drip for 24 hours.<sup>18</sup> Since these 2 schedules of penicillin dosage resulted in plasma penicillin concentrations of at least 10 units per cc. for variable periods of time in the case of the intramuscularly administered penicillin, and rather constantly in the case of the infused penicillin, it may be judged that these plasma concentrations of penicillin cause diffusion into the cerebrospinal fluid in some, but not all, patients. Therefore, an intravenous dose of penicillin was chosen for this study that would result in fleeting concentrations of from 30 to 70 units (average 49.64) units per cc. above 10 units for approximately 30

minutes<sup>13</sup> and above 1 unit for 2 hours. Attention is directed to the plasma concentrations existing at specific time intervals after the injection of the single dose of penicillin employed in this study because it is probable that there is a considerable lag between the time that penicillin first diffuses into the cerebrospinal fluid and the time that it is detected in the lumbar cerebrospinal fluid. Any delay in the appearance of penicillin in the lumbar cerebrospinal fluid is of importance in the treatment of meningitis. The appearance of penicillin in the cerebrospinal fluid within 2 hours after the initiation of therapy would be highly desirable and, if demonstrated, could be considered "prompt treatment" at the site of infection.

An interval of 2 hours after penicillin injection was arbitrarily chosen for sampling of the cerebrospinal fluid. Patients NT, MW and RMcL (Table 1) failed to show penicillin in the spinal fluid at 2 hours, but it was detected at 3 hours. Patient JC had no measurable penicillin in the spinal fluid at either 2 or 3 hours. Thus, 3 of the 4 patients who failed to show penicillin in the cerebrospinal fluid at the end of 2 hours did show it at 3 hours, the fourth case showing penicillin at neither of these times. In only 2 cases was the reverse true (SF, RM), penicillin being demonstrated at 2 hours and not at 3 hours. It seems probable, therefore, that the interval of 2 hours approximates rather closely the time required for the appearance of penicillin in the lumbar cerebrospinal fluid after the intravenous administration of 500,000 units of penicillin. More extensive sampling of the cerebrospinal fluid to determine the disappearance time of penicillin from the subarachnoid space was not done.

When the same dose of penicillin (500,000 units) was administered intravenously in conjunction with 3 gm.

of caronamide, the resulting penicillin plasma concentrations were enhanced so that transitory penicillin concentrations of from 60 to 104 units per cc. (average 95 units per cc.), above 5 units per cc. for 2 hours and above 2 units per cc. for 3 hours were reached in the average patient. These elevated concentrations of penicillin in the plasma resulted in doubling the amounts of penicillin demonstrated in the cerebrospinal fluid, and it can be observed that, in the 18 patients to whom the combination of drugs was administered, all showed penicillin in the spinal fluid at 2 and 3 hours. In an additional group of 25 patients penicillin appeared in the lumbar spinal fluid within 1 hour in every patient to whom 500,000 units of penicillin and 3 gm. of caronamide were given intravenously. Statistical analysis shows that the likelihood of the added elevations of penicillin in the spinal fluid following the combined use of penicillin and caronamide being due to chance alone is between 1 to 100 and 1 to 1000.

Clearly the elevation of penicillin concentrations in the plasma by the use of caronamide increased diffusion of penicillin into the cerebrospinal fluid, but it should be emphasized that the same results could be obtained without the aid of caronamide if sufficient penicillin was employed to give the same magnitude of penicillin plasma concentrations. Caronamide increased the penicillin plasma concentrations resulting from 500,000 units of penicillin from 2 to 5 times, these results conforming to those previously reported.<sup>1,6</sup> The intravenous administration of 3 gm. of caronamide was accompanied by no manifestations of toxicity, but about half the patients experienced a transitory generalized sensation voluntarily described as "itching". The rapidity of injection of a 15% solution of caronamide is the

most obvious explanation of this observation.

The amounts of penicillin observed in the cerebrospinal fluid were therapeutically significant, but perhaps minimal from the standpoint of relying upon them for the treatment of a purulent meningitis amenable to penicillin therapy. However, it should be stated that many systemic infections are treated without either attaining or maintaining in the plasma penicillin concentrations as high as those here observed in the cerebrospinal fluid. Since these levels were attained in the cerebrospinal fluid of normal individuals in whom the barrier between the blood and cerebrospinal fluid was less permeable than is the case in patients suffering from meningitis, much higher concentrations of penicillin might be anticipated in patients having inflammation of the meninges. This has proven to be the case in meningitis patients already studied and to whom 500,000 units of penicillin have been given intravenously. Penicillin concentrations in the cerebrospinal fluid

as high as 2 to 8 units per cc. have been observed within 2 hours after the first injection of penicillin.<sup>4</sup>

**Conclusions.** In a series of 21 patients who had uninflamed meninges, it has been shown that penicillin diffuses into the cerebrospinal fluid within 2 hours after a single intravenous injection of 500,000 units of penicillin. Three patients failing to show diffusion of the antibiotic into the cerebrospinal fluid after the intravenous administration of 500,000 units, showed measurable quantities of penicillin in the cerebrospinal fluid when caronamide was administered intravenously in conjunction with the same dose of penicillin. The observation that therapeutically significant levels of penicillin were attained in the cerebrospinal fluid in all of the patients here studied suggests that the parenteral and particularly intravenous administration of penicillin has a place in the therapy of purulent meningitis and that intrathecal injection of penicillin is unnecessary in the majority of patients.

The authors are indebted to the chiefs of the Neurological Services of the Philadelphia General Hospital for permission to study patients on their services, to Miss June Heckman for penicillin assays reported in this study, and to Mr. J. L. Ciminera for statistical analysis of data.

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# EFFECTIVE PENICILLIN THERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS AND OTHER CHRONIC INFECTIONS

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EMPIRIC methods are generally used as a guide for determining penicillin therapy. These range from arbitrary dosage schedules for certain infections to correlation of *in vitro* sensitivity of the etiologic organism with blood levels obtained during therapy as determined by assay with an unrelated species or strain of organism. These methods usually give therapeutically satisfactory results with highly sensitive organisms, but are often unsatisfactory when relatively resistant strains of bacteria are encountered.

To meet this deficiency, the technic of assaying the bacteriostatic activity of a patient's serum level during penicillin therapy with the isolated etiologic organism was introduced. This technic was initially developed in the course of studies of subacute bacterial endocarditis due to resistant strains of alpha hemolytic streptococci.<sup>3</sup> The success obtained in our hands has led to our use of this technic as a guide to effective therapy in septicemias secondary to a variety of acute and chronic suppurative conditions with satisfactory results. Its simplicity should make it practical for the small bacteriological laboratory, since for therapeutic purposes the standard assay

may be omitted. This report deals with the work done in establishing the validity of this technic.

**Methods.** Recently isolated organisms are subcultured to 2 or 3 suitable agar slants at the time the original sensitivities are determined, and stored at 4°C. for the duration of therapy for reference. Following determination of the sensitivity of the isolated strain, a dosage schedule is inaugurated to attain a minimum blood level of at least 4 times the indicated sensitivity. Calculations are based on the average levels found at stated intervals for standard dosages and methods of administration of the various penicillin preparations currently available.\*\* Usually 24 hours are allowed to elapse for stabilization of initial irregularities in absorption and excretion rate. When the intermittent method of administration is employed, adequate blood samples are aseptically drawn at the low point of the blood concentration curve, i. e., about 5 minutes before the next injection time.

The direct penicillin assay test is carried out as follows: Serial 2-fold dilutions of the patient's serum in broth are made in 8 sterile tubes ranging from undiluted to 1:128. A ninth tube, containing broth diluent only, serves as a control. The organism, isolated from the patient, previously grown in suitable broth for 6 to 18 hours at 37°C., or until the turbidity of the culture is equivalent to a concentration of approximately 600 million bacteria per cc., is used. We have found that total quantities of 1 cc. per tube with an inoculum of 0.05 cc. of approximately 1:1000 dilution of the isolated organism

\* These departments are supported in part by the Michael Reese Research Foundation.

\*\* In general, to maintain a level of 1 Oxford unit per ml. of serum, 1 million units by continuous drip (IV) or 1.5 to 2 million units by intermittent intramuscular injection are required. Caronamide and p-amino hippuric acid have both been successfully used to obtain elevated serum concentrations.

are convenient for pipetting and reading. After incubation at 37°C, for 18 hours, the highest dilution completely inhibiting growth is recorded. When micro-aerophilic or obligate anaerobic bacteria are encountered, the tubes are incubated under anaerobic conditions. The dosage is then adjusted in accordance with results obtained in the direct test. A re-check should be made 24 hours after any change in the therapeutic regimen.

**INTERPRETATION OF TEST.** Complete inhibition of growth in the first tube (undiluted serum) and slight growth in the second (1:2 dilution) is interpreted as the minimum satisfactory dosage which will be effective for the patient concerned and the specific organism involved. This concentration of penicillin has proven to be therapeutically satisfactory in our hands when maintained for considerable periods of time.

Since the bactericidal rate has frequently been found to be greatly accelerated at penicillin concentrations slightly higher than that resulting in complete bacteriostasis, we feel that a penicillin serum level producing complete inhibition in the first 2 tubes represents the optimal dosage to be maintained for the duration of either bacteriological or clinical evidence of active infection.

Inhibition at higher dilutions indicates that penicillin in excess of the optimal requirement is being administered, and the intervals or the number of units per injection may be regulated accordingly. We feel that any evidence of growth in the first tube indicates that the level is inadequate and should be at least doubled immediately despite previously ascertained sensitivity.

As evidenced by the Tables appended, this type of planned therapy, insuring serum levels sufficiently high to be completely bacteriostatic for the patient's own organism, has proved eminently satisfactory in the management of subacute bacterial endocarditis as well as in the control of vari-

ous other infections. In fact, not a single case of streptococcic endocarditis has failed to respond with complete clinical cure which we have treated in this manner during the past two years.

Table 1 presents the results of controlled therapy in 10 unselected cases of subacute bacterial endocarditis due to the *Streptococcus viridans* group treated at Michael Reese Hospital during the past 28 months. Clinical and bacteriological evidence of complete arrest were obtained in all but one of the early cases (Case 2) which was treated with inadequate amounts of penicillin. All patients were followed after discharge by periodic blood cultures for at least a year, and all have remained entirely symptom free to date. Thirty-four tests were performed in these 10 cases to establish the validity of these criteria of effective therapy. The amount of penicillin required for blood serum bacteriostasis varied from 1 to 32 times the broth concentration necessary as determined by direct assay. Some variation in the ratio in successive tests on the same patient was observed. Our impression is that these findings are more apparent than real because they may well be explained on the basis of the sources of error inherent in the serial dilution method of assay. Each reading actually represents a range, rather than an exact number, of units of penicillin. Case 5, which was followed over a longer period, however, shows a consistent slow drop in the ratio which suggests that a rising antibody titer may have had an enhancing effect.

Difficulty in obtaining adequate amounts of penicillin is largely responsible for fluctuations in levels of earlier cases. Not all dosage schedules were reduced to the minimum effective level, although uniform success with those which were decreased would indicate that others had been maintained



TABLE 1.—PENICILLIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS DUE TO ALPHA HEMOLYTIC STREPTOCOCCI

Case	Date	Standard Turbidity Test		Direct test with Patient's Organism													Ratio of Effective level of Sensitivity	Result of Therapy
		Sensitivity (in Oxford units)	Serum level (Oxford units/ml)	Und:1	1	2	1	1	8	1	16	1	32	1	64	1		
1 R B	10/20/45	5 0 I	10 24	+	+	+	+	+	+	+	+	+	+	+	+	+	4 1	Clinical cure 2 yrs 8 mos
	11/11/45		12 80	±	+	+	+	+	+	+	+	+	+	+	+	+		
	11/27/45	5 0 II	40 96	0	0	0	0	0	0	0	0	0	0	0	0	0		
	1/11/46		5 12 g	+	+	+	+	+	+	+	+	+	+	+	+	+		
2 H H	2/12/46	5 0 I	25 60	0	0	+	+	+	+	+	+	+	+	+	+	+	2 5 1	Blood stream periodically cleared
	2/27/46		2 56	not done														
	3/5/46		40 96	0	0	0	0	0	0	0	0	0	0	0	0	0		
	3/14/46		25 60	0	0	0	0	0	0	0	0	0	0	0	0	0		
	3/22/46		1 28	+	+	+	+	+	+	+	+	+	+	+	+	+		
	3/29/46		40 96	0	0	0	0	0	0	0	0	0	0	0	0	0		
	4/1/46	R 75 III 8 75 III 5 0 I }	40 96	{ 0	0	0	0	0	0	0	0	0	0	0	0	0		
	4/12/46	8 75 III	40 96	0	0	0	0	0	0	0	0	0	0	0	0	0		
	4/17/46	10 00 IV	12 80	+	+	+	+	+	+	+	+	+	+	+	+	+		
	4/21/46	15 00 V	20 48	+	+	+	+	+	+	+	+	+	+	+	+	+		
	4/26/46	17 50 VI	> 51 20 O	0	0	0	0	0	0	0	0	0	0	0	0	0		
	4/29/46	17 50 VI	40 96	0	0	0	0	0	0	0	0	0	0	0	0	0		
3 R C	6/19/46	0 31	6 40	0	0	0	0	0	0	0	0	0	0	0	0	0	Died	
7/8/46		↑ 12 80	0	0	0	0	0	0	0	0	0	0	0	0	0			
4 I h	7/30/46	0 02	0 64	0	+	+	+	+	+	+	+	+	+	+	+	+	Clinical cure 1 yr 10 mos	
5 J N	9/3/46	0 156 I	1 56	0	0	0	0	0	0	0	0	0	0	0	0	0	2 1	Clinical cure 1 yr 8 mos
	9/17/46		0 64	0	0	0	0	0	0	0	0	0	0	0	0	0		
	(therapy stopped - 2 positive cultures)																	
	10/11/46	0 156 II	0 80	0	0	0	0	0	0	0	0	0	0	0	0	0		
	10/24/46		0 80	0	0	0	0	0	0	0	0	0	0	0	0	0		
11/1/46		5 12 f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	
6 H T	12/9/46	0 02	0 16	0	0	0	0	0	0	0	0	0	0	0	0	0	Clinical cure 1 yr 6 mos	
			↓ 0 08	0	±	+	+	+	+	+	+	+	+	+	+	+	2 1	
7 H P	3/25/47	0 02	1 28	0	0	0	0	0	0	0	0	0	0	0	0	0	16 1	Clinical cure 1 yr 2 mos
8 T M	7/18/47	0 02	6 40	0	0	0	0	0	0	0	0	0	0	0	0	0	5 1	Clinical cure 10 mos
9 H B	4/27/48	0 04	6 40	0	0	0	0	0	0	0	0	0	0	0	0	0	2.5 1	Clinical cure 2 mos
5/1/48			↓ 2 56	0	0	0	0	0	0	0	0	0	0	0	0	0	2 1	
10 A F	5/7/40	0 04	2 56	0	0	0	0	0	0	0	0	0	0	0	0	0	1 1	Clinical cure 1 mo
5/25/48			2 56	0	0	0	0	0	0	0	0	0	0	0	0	0	1 1	

Roman Numerals = Succeeding isolations

0 = no growth

# peak level at 5 minutes

↑ dose increased

↓ dose decreased

+ = growth

# level obtained with concurrent administration of p-amino hippuric acid

at unnecessarily high concentrations. At these higher levels, complete inhibition of the organism was obtained in all dilutions within the effective range. Pertinent comments on cases of special interest follow; the remainder made uneventful recoveries on dosage schedules shown to be effective by the direct test. Blood cultures taken during therapy were uniformly negative with added Clarase, except where indicated by Roman numerals for later isolations.

CASE 1 (Table 1). R. B. This 17-year-old boy had been treated elsewhere on several occasions with the usual empiric type of therapy, each time followed by clinical relapse with isolation of an alpha hemolytic streptococcus from the blood stream. Since levels of 10 Oxford units per ml. proved ineffective when tested against his own organism and positive blood cultures were obtained during therapy, the dose was markedly increased. A concentration of 20 Oxford units was found by direct test to be necessary for complete bacteriostasis. Maintenance of levels above this critical point for protracted periods of time resulted in complete arrest of the infection despite a concurrent attack of appendicitis requiring surgery. Three weeks after discharge a level of 5 Oxford units per ml., obtained during prophylactic therapy for oral surgery, was tested against the initially isolated strain of streptococcus with the predicted result. This case has been fully reported elsewhere<sup>2</sup>.

CASE 2 (Table 1). H. R. The alpha hemolytic streptococcus strain isolated from blood cultures on this 75 year old male developed *in vivo* resistance to penicillin, probably because treatment, extending over several months, was periodically interrupted, and at times seriously reduced due to lack of penicillin supply. During periods of effective therapy, as established by direct test, repeated blood cultures were sterile. When therapy was inadequate or interrupted, blood cultures became positive again. All strains thus isolated were identical culturally and biochemically, except for the gradual increase in penicillin resistance. The patient died as a result of renal and pulmonary complications following a two-stage prostatectomy. Permission for autopsy was not obtained.

CASE 3 (Table 1). R. C. The concentration of penicillin in the blood stream was temporarily increased pending identification of bacterial growth in a single routine blood

culture flask. *Staphylococcus albus* was isolated which was judged to be a contaminant. Dosage was reduced to the former level, and recovery was uneventful.

CASE 4 (Table 1). I. K. The direct test showed that an unusually high ratio of effective serum level to penicillin sensitivity of the isolated strain (32:1) was necessary for complete bacteriostasis. The penicillin sensitivity of this organism was well within the usual range for this species. Corroborative evidence was obtained from the results of a blood culture drawn simultaneously with blood taken for level, 24 hours after initiation of therapy. Flasks with added Clarase were positive, but those without remained negative. All subsequent cultures were negative and recovery was uneventful.

CASE 5 (Table 1). J. N. The first course of penicillin given was too short in duration, and blood cultures were positive within a week following cessation of therapy. The fact that the blood level was adequate, as determined by the direct test, was verified by the satisfactory response to a second full course of therapy (5 wks.) with maintenance of a somewhat lower serum level. Blood cultures were consistently negative for 1 year following discharge as clinically cured.

Several cases of septicemia due to hematogenous spread of organisms from foci of acute and chronic infection are presented in Table 2. *Staphylococcus aureus* infections were mainly selected for further investigation of the efficacy of this type of controlled therapy because of the relatively high initial sensitivity to penicillin of many strains of this species and the tendency for occasional strains to increase progressively in resistance when inadequately treated. In one case (H.W.) a highly resistant alpha hemolytic streptococcus was completely controlled by this method.

CASE 1 (Table 2). H. W. Septicemia was probably secondary to chronic foci of infection in the lungs. Blood cultures were negative during the period of adequate therapy as determined by direct test, but became positive when the penicillin concentration was allowed to drop too soon. Re-establishment of the effective level for a longer period permanently sterilized the blood stream. Death occurred from bronchogenic carcinoma with metastasis, without recurrence of the septicemia. At autopsy no evidence of vascular in-

TABLE II.--PENICILLIN THERAPY OF ACUTE AND CHRONIC INFECTIONS WITH HEMATOGENOUS SPREAD

Case	Etiological Agent	Date	Standard Turbidity Test		Direct Test with Patient's Organism										Ratio of Effective Level to Sensitivity	Diagnosis Outcome of Therapy		
			Sensitivity in O.u.	Serum level in O.u./ml.	Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128						
1. H.W.	alpha hemol. Streptococcus	1/14/46	10.0 I	12.80	+	+	+	+	+	+	+							
		1/17/46		40.96	0	+	+	+	+	+	+							
		1/19/46	10.0 II	25.60	+	+	+	+	+	+	+							
		1/23/46		40.96	0	+	+	+	+	+	+							
2. H.D. (child)	Staphylococcus aureus	5/17/46	0.15	3.20	0	0	0	0	0	0	+	+				4:1	Septicemia, complete arrest; death from other causes.	
3. M.R. (child)	Staphylococcus aureus	11/16/46														1.5:1	Septicemia Osteomyelitis: disch. as cured	
4. D.K.	Staphylococcus aureus (2nd adm.)	11/18/46	0.15		+	+	+	+	+	+	+	(empiric therapy)						
		1/5/47	0.31 I	0.08 3.20	0	+	+	+	+	+	+	+						
5. H.W.	Staphylococcus aureus	10/22/47	1.25 II	20.00	0	0	0	0	0	0	0	+	+				21:1	Septicemia Osteomyelitis: disch. as cured
		10/27/47		§ -	(0.625 u. streptomycin)												8:1	Septicemia Prostatitis
		10/1/47		§ -	0	0	0	0	0	0	0	0	+	+				
		10/2/47			0	0	0	0	0	0	0	0	0	0	+	+		
		10/9/47	.625	1.28	0	+	+	+	+	+	+	+						
		10/13/47		** 1.28	0	+	+	+	+	+	+	+					2:1	Septicemia, chronic osteomyelitis: Septicemia cured, disch.
6. L.R. (baby)	Staphylococcus aureus	10/17/47		** 2.56	0	+	+	+	+	+	+	+	+	+	+	+	2:1	Septicemia cured, disch.
		10/17/47		1.28	+	+	+	+	+	+	+	+	+	+	+	+	2.5:1	Draining sinus
		1/7/48	.625†	3.20 3.20	0	0	0	0	0	0	0	+	+				2.5:1	Septicemia Pulmonary abscess Osteomyelitis: disch. as cured
7. Baby R (Premature)	Staphylococcus aureus	12/3/47	.31 I	(Empiric therapy)													1:1	Septicemia
		12/8/47	.625 II	0.80 qns	+	+	+	+	+	+	+	+	+	+	+	+		
		12/10/47		5.12	0	0	0	0	0	0	0	0	+	+				
8. Penicillin and Streptomycin (See case discussions)	Staphylococcus aureus	1/11/48	2.5 I	(0.625 u. streptomycin)														
		1/14/48			0	0	0	0	0	0	0	0	0	0	0	0	+	
		1/27/48	2.5 II (> 80 u. streptomycin)	§ -	0	0	0	0	0	0	0	0	0	0	0	0	+	
9. Romansky formula, 8 & 12 hrs. respectively	Staphylococcus aureus	2/5/48	2.5 II	6.40	0	0	0	0	0	0	+	+						
					0	+	+	+	+	+	+	+	+	+	+	+	+	1.5:1

§ - no growth  
- growth

§ Penicillin and Streptomycin (See case discussions)

† Roman sky formula, 8 &amp; 12 hrs. respectively

‡ Dose increased

0 = no growth

+ = growth

fection could be found, so presumably the intensive therapy had been effective.

CASES 2 and 3 (Table 2). Of notable interest is the marked difference in ratio of effective serum penicillin concentration during therapy to the sensitivity of the strains of *Staphylococcus aureus* isolated from blood cultures of these two otherwise essentially similar cases (1.5:1 and 20:1, respectively). In Case 3 (M. R.) septicemia developed during empiric therapy, which was shown by the direct test to be inadequate. Sharply increasing the dosage to serum levels completely bacteriostatic for the isolated strain resulted in complete recovery. Both patients were discharged as cured.

CASE 4 (Table 2). D. K. Acute septicemia and meningitis developed following a partial prostatectomy in this 65 year old male. Subsequent penicillin dosage was shown to be more than adequate by the direct test. Blood and spinal fluid cultures became negative, and therapy was stopped. Intermittent low grade chronic septicemia subsequently developed, and the patient was treated with small empiric doses of penicillin alternated with sulfonamide drugs both in the hospital and at home without complete eradication of the infection. Some months later he was readmitted for study. Apparently the same strain of hemolytic *Staphylococcus aureus* was again cultured from peripheral blood, but its resistance to penicillin had increased 4-fold. Since the organism was sensitive to streptomycin, combined therapy was instituted, and the antibiotic level of the blood serum was demonstrated to be adequate to control the infection. Therapy was continued for a longer period, and the patient discharged with no further recurrence of the septicemia.

CASE 5 (Table 2). R. W. Septicemia developed secondary to chronic osteomyelitis, with a draining sinus. Penicillin levels demonstrated to be adequate for control were maintained until complete control of the infection was obtained. Prophylactic levels during a later admission for surgery to the sinus were satisfactory when tested against a similar strain of *Staphylococcus aureus* isolated from the drainage. Recovery was satisfactory without recurrence of the septicemia, and the patient discharged.

CASE 6 (Table 2). L. R. This 3 weeks old baby was admitted for cellulitis of the finger and possible pneumonitis. *Staphylococcus aureus* was isolated from the excised finger and blood stream. Empiric therapy based on age and weight was instituted. A second blood culture drawn during therapy was again positive for *Staphylococcus aureus*, but its sensitivity to penicillin had decreased.

The patient's serum had 4 + growth in 1:2 dilution (undiluted serum, quantity insufficient) and the dosage was increased immediately. In the meantime a lung abscess and several foci of acute osteomyelitis had developed. A second test at the new dosage schedule established that therapy was more than adequate for control of the organism, and it was maintained at this level for 3 weeks. Subsequent blood cultures were sterile, and gradual resolution of all foci of infection, without surgical intervention, took place. In an attempt to hasten resolution and prevent possible secondary invaders from the lung abscess, streptomycin was given later in addition to penicillin. All roentgenograms were normal at time of discharge and follow-up blood cultures negative.

CASE 7 (Table 2). Baby R. This one day old premature infant was admitted to the hospital following home delivery without medical attention with a cord stump infection and meningitis symptoms. *Staphylococcus aureus* was cultured from the umbilicus, spinal fluid and peripheral blood. Pending identification of the isolated bacteria, both penicillin and streptomycin were given. Both drugs were continued because of the relatively high resistance to penicillin *in vitro*. The combined antibiotic blood serum level was more than adequate for control when tested directly and the spinal fluid and blood stream rapidly became sterile. Therapy was discontinued, evidently too soon. Multiple foci of acute osteomyelitis developed, and the blood culture became positive once more. Sensitivity to penicillin was unchanged, but the organism was now resistant to 80 micrograms of streptomycin. Penicillin therapy was resumed with blood serum levels shown by the direct test to be adequate for control of the infection, providing good penetration into infected areas could be obtained. Unfortunately, other foci appeared throughout the body. A week later knee aspiration cultures yielded a third isolation of *Staphylococcus aureus*. Penicillin sensitivity remained the same (2.5 Oxford units) and sensitivity to streptomycin had apparently decreased to 10 micrograms since withdrawal of this antibiotic. Despite continued therapy the clinical course became progressively worse, and the patient died. Undoubtedly, prematurity and debilitation as well as insufficiently prolonged treatment in the early stages were contributory factors in the failure of therapy in this infant.

Comment: In spite of one frank failure, in our opinion there is definite value in using this type of planned therapy, especially in cases of staphylo-

coccic osteomyelitis in children. Antibiotic therapy in no way obviates the necessity for indicated surgical procedures, particularly where sequestra have formed and in relatively avascular foci. During the early acute stage of osteomyelitis, antibiotic therapy has proven effective as the only adequate therapeutic measure, assuming that blood serum concentrations demonstrated to be adequate for complete bacteriostasis of the patient's own organism are maintained for sufficient periods of time. In our opinion sterile blood cultures are not, *per se*, adequate criteria for cessation of therapy.

Our procedure is not routinely used for relatively sensitive organisms found in transient bacteremias and acute infections where the effectiveness of therapy is readily evidenced by the clinical response of the patient. As a control, however, in further study of the relationship between effective penicillin serum concentrations and *in vitro* sensitivity, several such cases were investigated (Table 3, Group A). All were acute septicemias treated with penicillin following isolation of a sensitive organism from peripheral blood. Although variations in the ratio of effective serum level to sensitivity were noted, the range was less marked. All infections promptly subsided following therapy, and repeat blood cultures were negative before discharge.

The last 3 cases (Table 3, Group B) further illustrate the utility of this method for controlling therapy in the treatment of resistant organisms, or mixed infections, especially when the use of more than one antibiotic is indicated. Immediate direct test of the bacteriostatic property of both spinal fluid and blood serum during various types of combined therapy has proven very valuable, pending results of individual sensitivity tests with subsequent elimination of non-contributory drugs.

There are two cardinal principles

in the effective treatment of sub-acute bacterial endocarditis and similar septic conditions with penicillin; namely, the amount and the duration of therapy. The latter is beyond the scope of this report, except in so far as optimal therapy may be expected to shorten the duration. In general it has been our experience that 4 to 5 weeks are usually necessary to insure complete, permanent arrest, but no objective criteria have yet been found.

The amount of penicillin to be given will depend upon the minimum blood serum concentration desired. The effective blood level appears to us to be the resultant of 3 sets of variable factors. First, and subject to a certain degree of control, are route of administration, vehicle employed, number of units and interval of each injection, and the use of artificial kidney blocks. A second group, subject to a greater degree of variability, is inherent in the individual patient: rate of absorption, rate of excretion and status of kidney function, inactivation by binding with plasma proteins,<sup>4</sup> and specific antibody production. A third group concerns properties inherent in the individual bacterium such as growth requirements, metabolism, and reaction to antibiotics. In addition to the *in vitro* sensitivity as usually defined, is the unpredictable variation observed in the concentrations of assayable penicillin which must be achieved in patients' sera in order to obtain the same degree of bacteriostasis. Eagle<sup>1</sup> in his excellent discussion of the therapeutic significance of blood penicillin levels, calls attention to two additional factors of possible significance in this respect. Concentrations of penicillin slightly above the minimal bacteriostatic level appear to increase the *rate* of death of the susceptible organism; greatly increased concentrations, on the other hand, paradoxically appear

TABLE III.--ANTIBIOTIC THERAPY IN ACUTE SEPTICEMIA DUE TO VARIOUS SPECIES OF PATHOGENIC BACTERIA																				
Case	Etiological Agent	Date	Standard Turbidity Test		Sensitivity in O u.	Serum level in O.u./ml.	Direct Test with Patient's Organism												Sensitivity	Outcome
			Sensitivity in O u.	Serum level in O.u./ml.			Serum Dilutions													
							Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128						
Group A Penicillin Therapy																				
1. S.h. Staphylococcus aureus		1/4/47	2.5	20.48			0	0	0	0	+	+	+	+	1:1	Bacteremia Recovered				
2. D.B. Type 18 Staphylococcus albus		6/4/47	.0025 .31 .31	Treated empirically: no level taken 10.24			0	0	0	0	0	+	+	+	2:1	Bacteremia Pneumonia Recovered				
3. A.L. "minute" hemol. Streptococcus		10/7/47	.04	.64			0	0	0	0	0	+	+	+	1:1	Septicemia Acute Rheu. Arthritis Recovered				
4. M.S. beta hemol. Streptococcus		3/10/48	.02	2.56			0	0	0	0	0	+	+	+	8:1	Septicemia Thrombophlebitis Recovered				
Group B Combined Therapy																				
1. N.B. Staphylococcus (child) aureus		10/14/47	.15	(.625 u. streptomycin) Spinal fluid 0			0	0	0	0	0	+	+	+		Brain abscess outside pt. not followed				
2. T.N. Staphylococcus (child) aureus		3/27/47	5.0	(.625 u. Streptomycin) blood serum 0			0	0	0	0	0	+	+	+		Septicemia. Extensive burns. Sept. controlled. Death due to burns				
3. L.G. Hemophilus (child) influenzae		4/20/48	1.25	(2.5 u. Streptomycin) spinal fluid 0			0	0	0	0	0	+	+	+		Meningitis Recovered				

0 = No growth

+ = Growth

↗ = Dosage increased

0 = No growth  
+ = Growth  
↑ = Dosage increased

to decrease the death rate of certain strains of streptococci.

Many, if not all, of these variables are susceptible to individual evaluation, but the methods are both time consuming and tedious. Assay of the effective blood serum penicillin concentration by using the organism isolated from the patient under treatment offers a direct, rapid and relatively accurate means of evaluating adequacy of therapy. By this method the minimal effective level is that concentration of assayable blood serum penicillin which can be shown to be completely bacteriostatic for the strain isolated. We believe the optimal therapeutic level should be at least twice the minimal effective level, as shown by our direct test. Penicillin dosage schedules should be adjusted to maintain the necessary blood serum concentration for extended periods of time.

**Summary and Conclusions.** 1. A direct test for determining the therapeutic value of penicillin levels by as-

say with the strain of bacteria isolated from the patient under treatment is described.

2. Minimal and optimal effective blood serum penicillin concentrations applicable to therapy of subacute bacterial endocarditis and infections due to relatively resistant strains of bacteria are defined.

3. It is recommended that penicillin therapy in such cases be based on maintenance of adequate serum levels as judged by the direct test for considerable periods of time.

4. It is further recommended that unnecessarily high levels are not only economically wasteful, but may possibly result in prolonging the duration of therapy by reducing the bactericidal rate of the strain involved.

5. Evidence is presented to prove that this type of planned therapy is a valid and effective basis for treatment of subacute bacterial endocarditis and chronic infections due to relatively resistant strains of susceptible organisms.

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# PERICARDIAL EFFUSION: A CONSTANT, EARLY AND MAJOR FACTOR IN THE CARDIAC SYNDROME OF HYPOTHYROIDISM (MYXEDEMA HEART)\*

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SINCE Zondek's<sup>31</sup> first report in 1918, it has been recognized that a certain number of patients with myxedema develop cardiac phenomena that have been designated "myxedema heart." These include: (1) a great increase in the size of the cardiac dulness on percussion, and of the cardiac shadow on fluoroscopy and in the roentgenogram; (2) faintness of the heart sounds on auscultation; (3) diminished minute volume of cardiac output; (4) feeble cardiac pulsations as seen fluoroscopically; (5) reduced voltage in the electrocardiogram, especially of T-waves that are flattened or even inverted and at times a shortened Q-T interval; and (6) complete reversibility of these changes to normal under treatment with thyroid hormone.

These phenomena have usually been attributed by clinicians to a uniform dilatation, cryptic in nature, of all cardiac chambers. The electrocardiographic changes, as Bellet and McMillan<sup>1</sup> state, have been explained by alterations in the myocardium and by easier dissipation of the cardiac

action current through myxedematous tissue. Pathologists have little to say on the subject: as Boyd<sup>3</sup> points out, the lack of autopsy material is responsible for our dearth of accurate knowledge. Boyd's own experience includes no necropsy and only 1 patient studied by Roentgen-ray.

An occasional roentgenologist has commented on the similarity of the roentgenologic phenomena in these cases to those of pericardial effusion. Thus, Ungerleider and Gubner<sup>28</sup> suggest that when *marked* enlargement is present, pericardial effusion should be suspected. They point out that an effusion could largely or entirely explain such findings as the increased size of the cardiac shadow, the diminished amplitude of the cardiac pulsations, the faint heart sounds and even the electrocardiographic changes.

Yet there are on record comparatively few instances of the proved presence of pericardial effusion in patients with myxedema. Gordon<sup>12</sup> in 1929 reported the first case and in 1935 discussed the subject before the Associ-

\* Read in abstract before the Association of American Physicians in Atlantic City, N. J., on May 4, 1948.



ation of American Physicians.<sup>13</sup> Since then, an additional 16 publications bring to 21 the total number of recorded cases, 16 proved during life by pericardial tap and 5 found at necropsy. Only Scherf<sup>25</sup> has observed as many as 3 cases, and ventures the belief that pericardial effusion is often present "in the large hearts of myxedema". Harrell and Johnston<sup>14</sup> report 2 patients with positive taps. Lerman, Clark and Means<sup>19</sup> cite post-mortem records in which 2 of 5 myxedema cases were found to have pericardial effusions. All the others<sup>2,4,5,8,9,10,15,17,18,20,21,23,29</sup> are single case reports, sometimes one of a number (up to 20) of cases of myxedema heart studied by these authors. Without exception, the cases with proved effusion were those in which a very large cardiac size or shadow gave the clue to effusion and suggested a diagnostic tap.

The prevailing clinical view, therefore, is that pericardial effusion is only rarely a contributory factor to the enlargement of the cardiac silhouette in this disease.<sup>30</sup> In a group of 4 consecutive cases of myxedema we have made observations which we think warrant a revision of this view.

**Case Reports.** CASE No. 1. Mrs. S. M., a white woman, aged 61 years was admitted to this hospital on Jan. 30, 1917, with a chief complaint of a swollen face and easy fatigability. In 1935, because of thyrotoxicosis, she had been subjected in this hospital to a thyroidectomy. At that time the heart was of normal size. (Fig. 1a).<sup>\*</sup> Several months later she noticed that she tired easily, was short of breath on exertion, was constipated and began to gain weight. The presence of myxedema was recognized and thyroid treatment instituted with good results. During the succeeding years she was observed from time to time in the Out-Patient Department and did well or not so well, depending on her observance of treatment. For some weeks prior to the present admission she had taken no thyroid.

Physical examination showed an obese (165½ pounds, height 62 inches) elderly woman with the typical heavy facies of myx-

edema. The skin was dry and the hair dry and brittle. The cardiac dulness was greatly enlarged, the apex beat not visible; the sounds were faint and there was a soft systolic murmur. The blood pressure was 138/90 and the pulse 80 to 90. Although she had dyspnea on exertion, there were no objective signs of cardiac failure: the lung bases showed no rales, the liver was not enlarged and there was no edema of the feet or ankles.

**Laboratory data:** Basal metabolic rate—18%, blood cholesterol 680 mg. per 100 cc., serum protein 7.5 gm., serum albumin 4.7 gm., serum globulin 2.8 gm., A/G ratio 1.7; inorganic phosphorus 3.4 mg., alkaline phosphatase 2.4 units; blood count: erythrocytes 4,700,000, hemoglobin 12 gm., leukocytes 6800 (neutrophils 53%, lymphocytes 37%, monocytes 2%, eosinophils 5%, basophils 3%); urine analysis: Sp.gr. 1020, albumin 1+, other findings normal.

The electrocardiogram (Fig. 5A) showed somewhat reduced voltage of the complexes, a P-R interval of 0.18 second, and negative T-waves in the limb leads and in CR4 and CR5: "findings compatible with hypothyroidism".

A routine chest film (Fig. 1b) showed a huge heart shadow, and by fluoroscope the cardiac pulsations were seen to be sluggish and small. The roentgenologist made a diagnosis of cardiac dilatation.

However, the faintness of the heart sounds and lack of an apex impulse suggested to one of us (L.A.S.) the presence of a pericardial effusion. A pericardial puncture yielded 310 cc. of a straw-colored fluid which was replaced with an equal amount of air. Now the roentgenogram (Fig. 1c) showed a heart comparable in size to that of 12 years before, within a greatly distended pericardium that still contained much fluid. The pericardial sac had a thin wall that certainly was not edematous. Under the fluoroscope the normal-sized heart showed hyperactive pulsations within the pneumo-hydro-pericardium, quite different from the feeble pulsations of the silhouette seen before tapping.

**Course:** Treatment with thyroid substance was then begun, with good results. On Feb. 25, 1917, 26 days after admission, her metabolic rate was +4% and the cholesterol 258 mg. At the same time the cardiac outline diminished markedly, with disappearance of the pericardial effusion (Fig. 1d). There was also a return toward the normal in the electrocardiogram (Fig. 5B).

We have observed this patient in two additional periods of hypothyroidism, induced with her consent by omitting treatment. In

\* All chest roentgenograms here used are 4 foot films, not teleoroentgenograms.

January, 1948, when she had been without medication for several weeks, she had gained 20 pounds, her cardiac dullness was enlarged and the heart sounds were feeble. The roentgenogram showed again an increased cardiac shadow. Paracentesis again showed the presence of a straw-colored effusion in the pericardial sac. Under thyroid treatment there was again return to normal in the several findings. In a second period of low metabolism 2 months later there was clinical and roentgenological evidence of pericardial effusion, but we did not feel justified in doing another tap.

She is now being kept in a euthyroid state and has no apparent cardiac abnormality.

These observations led us to think promptly of the possibility of pericardial effusion in the next patient with myxedema whom we encountered.

CASE No. 2. Mrs. J.M., a white woman aged 67, was seen in 1947 because of chief complaints of dizziness, lassitude and intolerance of cold. In 1923 she had a partial thyroidec-tomy because of thyrotoxicosis that had involved a weight loss of 106 pounds. In 1935

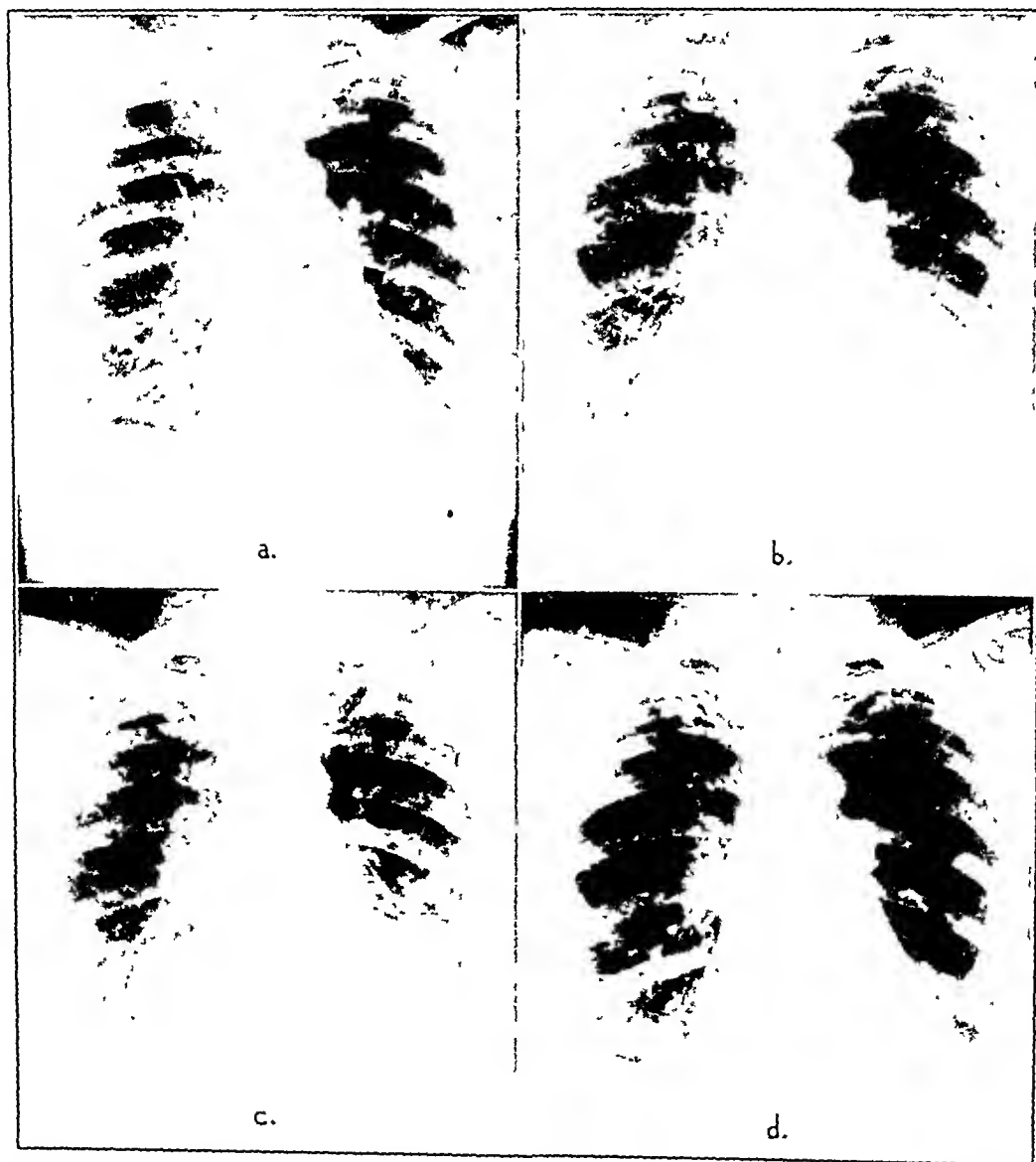


FIG. 1.—Case 1: "Cardiac" silhouettes in myxedema. (a) Routine chest film in 1935 when patient, then aged 49, had thyrotoxicosis, (b) January, 1947; patient myxedematous. Roentgenologic diagnosis: "cardiac dilatation". But pericardial tap yielded 310 cc. of fluid which was replaced (c) with air. Note thin line of pericardium, not edematous. (d) Three weeks later, after thyroid medication, "heart size within normal limits".

there were renewed evidences of thyrotoxicosis for which she received irradiation of the thyroid, with resultant improvement. In 1943 the myxedema began that brought her to us 4 years later.

*Physical examination* showed a short fat woman (61 inches, 161 pounds) in no distress. The face was puffy and the hair dry. The cardiac dulness was greatly enlarged, the heart sounds were feeble, and there was a soft mitral systolic murmur. There was no evidence of circulatory failure: no basal rales, hepatic swelling or peripheral edema. The blood pressure was 96/56 and the pulse rate 86.

*Laboratory data:* Basal metabolic rate—25%, serum cholesterol 420 mg. per 100 cc.; blood count: 3,900,000 erythrocytes, 12.6 gm. hemoglobin, 4800 leukocytes; urine findings within normal limits.

**CASE 3:** Mrs. V.H., a white woman of 58 years, was admitted in June, 1947, because of post operative myxedema. In 1940 she had had a subtotal thyroidectomy for thyrotoxicosis, and in the years that followed she gained 60 pounds in weight.

*Physical examination* showed an obese subject (198 pounds, 64½ inches) with no other positive findings. The blood pressure was 130/80, the pulse 72. The precordial dulness was not much enlarged, but the heart sounds were of fair quality. There were neither signs nor symptoms of any cardiac failure.

*Laboratory studies:* A basal metabolic rate of -18%, serum cholesterol 608 mg. per 100 cc., normal blood count and urine findings, a normal sugar tolerance curve.

The electrocardiogram showed upright P-waves, P-R interval 0.14 second, low voltage in all leads, T-waves low in all leads.

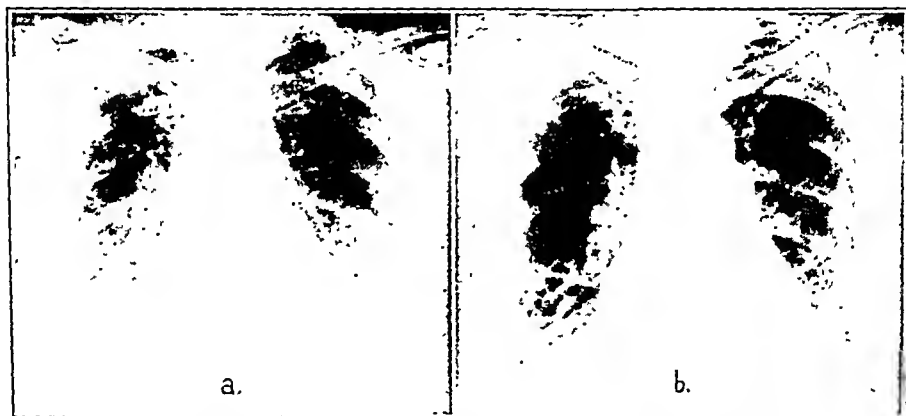


FIG. 2.—Case 2: (a) Chest film after removal of 150 cc. of pericardial fluid and replacement with air in myxedematous patient. (b) Diminished heart size after 6 weeks of thyroid medication.

Under the fluoroscope the large heart size was confirmed.

The electrocardiogram showed low voltage in all leads, P-waves upright in all leads, P-R interval 0.16 second, QRS not remarkable, T-waves diphasic in Leads I and II and in the precordial leads.

Pericardial tap yielded 150 cc. of straw-colored fluid that was replaced with air. The roentgenogram (Fig. 2a) showed the presence of considerable residual fluid and again a thin non-edematous pericardium.

*Course.* Six weeks later under thyroid treatment she was much improved: her weight had dropped to 147, the basal metabolic rate was -10%, the serum cholesterol 240 mg. The electrocardiogram showed increased voltage of the complexes and upright T-waves, and the roentgenogram showed a definite decrease in the heart size (Fig. 2b).

The roentgenogram (Fig. 3a) was reported as showing the heart to be "moderately but definitely enlarged, with nothing characteristic in the configuration. The enlargement is apparently both right and left sided. We understand that pericardial effusion is considered from the clinical standpoint, but from the Roentgen standpoint we feel unable either to confirm or rule out this impression."

A pericardial tap nevertheless yielded 150 cc. of a straw-colored fluid.

Three weeks later, under thyroid treatment, she had a basal metabolic rate of -3%, a serum cholesterol of 350 mg., a normal electrocardiogram and a normal-sized heart shadow (Fig. 3b).

**CASE 4:** Mrs. M.S., a white woman aged 62 years, was admitted to hospital on February 16, 1948, because of failing vision due to cataracts. For 7 years she had been gaining

weight, was easily fatigued and lost a good deal of hair. She had also had definite anginal symptoms, with precordial pain radiating to the neck and left arm upon exertion.

*Physical examination* showed, in addition to obesity and cataracts, an enlarged cardiac dulness with feeble heart sounds, a soft sys-

cc.; blood count: 3,400,000 erythrocytes, 9.9 gm. hemoglobin, 4900 leukocytes with a normal differential count; urine: a trace of albumin; serum protein 6.4 gm., serum albumin 4.0 gm., globulin 2.4 gm., calcium 10.6 mg.

The electrocardiogram showed low voltage,

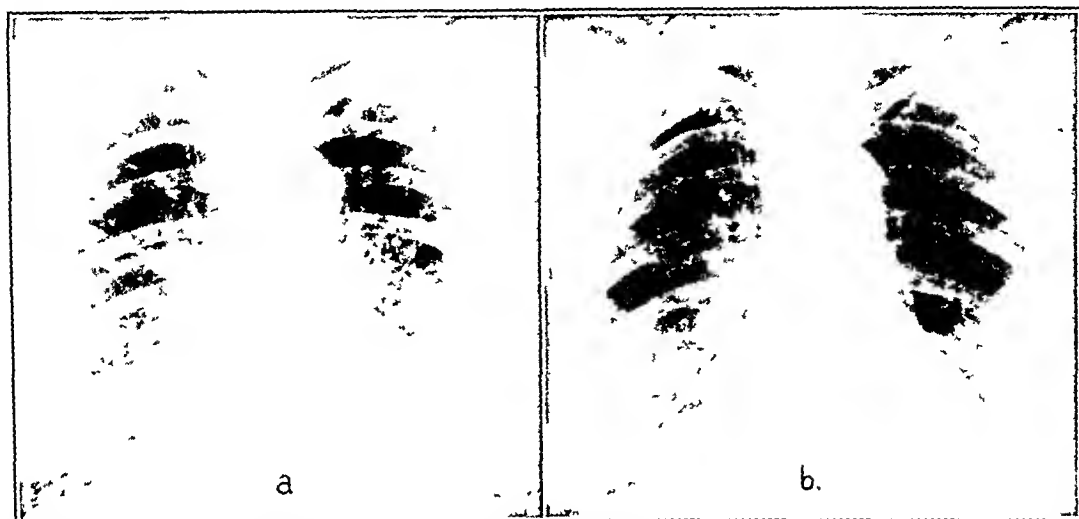


FIG. 3.—Case 3. (a) Chest film of myxedematous patient, cardiac shadow does not suggest presence of pericardial effusion, yet tap yielded 150 cc. of fluid. (b) Three weeks later, under thyroid medication, normal heart shadow.

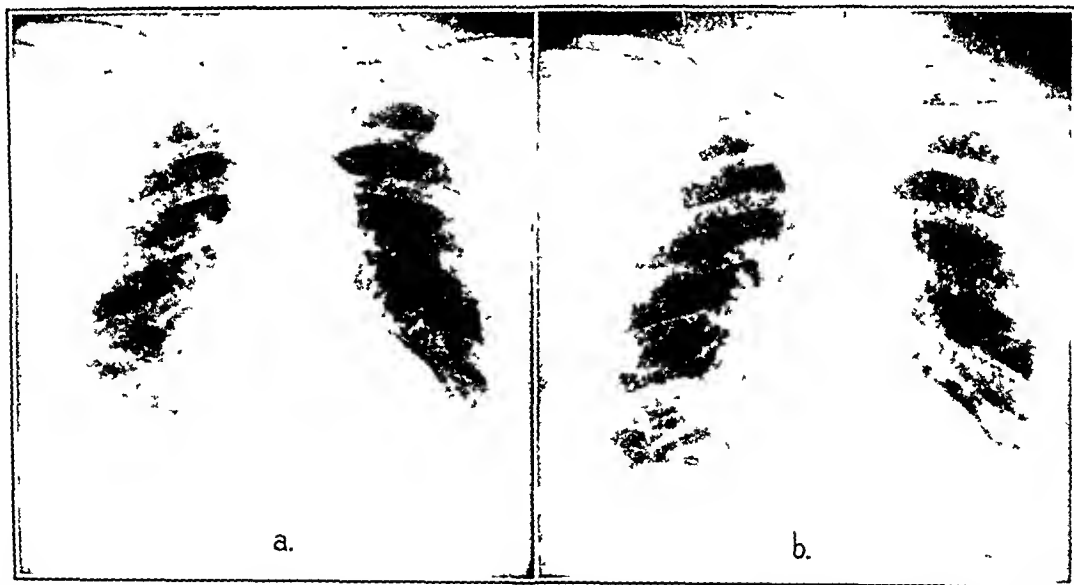


FIG. 4.—Case 4: (a) Chest film of myxedematous patient; roentgenologic diagnosis: "enlarged heart shadow, especially left ventricle, no pericardial effusion". But tap yielded 105 cc. of fluid, which was replaced (b) with air. Note thin line of pericardium.

toic mitral murmur and no palpable cardiac impulse. The blood pressure was 120/74 and the pulse 86.

*Laboratory data:* A basal metabolic rate of -42%, serum cholesterol 37.0 mg. per 100

upright P-waves, P-R interval 0.16 second, flat T-waves and QRS changes suggesting coronary insufficiency.

The roentgenogram showed an enlarged heart shadow, and the roentgenologist spoke

of a large left ventricle and an "aortic configuration", but made no mention of possible pericardial effusion (Fig. 4a).

Since the clinical diagnosis of spontaneous or primary myxedema was established, it was decided to perform a pericardial paracentesis. The tap yielded 105 cc. of straw-colored fluid like that of the other 3 cases. The fluid was replaced with an equal amount of air and another film made (Fig. 4b) that again made visible the thin-walled pericardium.

silhouette definitely diminished in size. A cataract extraction was performed without mishap.

Here, then, are 4 consecutive cases of myxedema in each of which the presence of a considerable pericardial effusion was proved. Yet none had any evidence of congestive heart failure and 2 of the 4 had relatively little

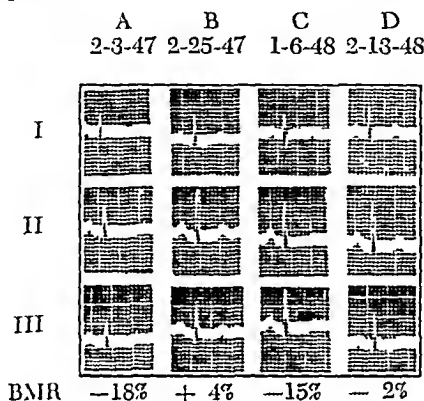


FIG. 5.—Electrocardiographic findings in Case 1 during (A, C) 2 periods of low metabolism (pericardial effusion proved by tap in each period) and (B, D) 2 periods of normal metabolism after thyroid medication. Note T wave changes and low voltage in (A) and (C), and improvement in these points in (B) and (D).

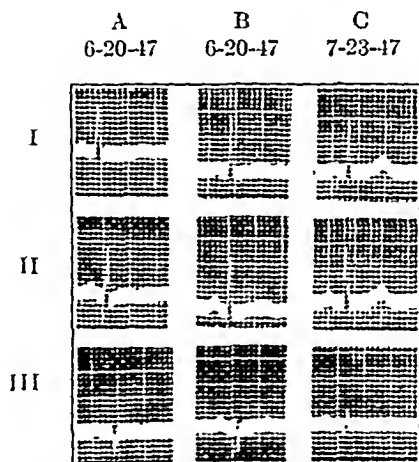


FIG. 6.—Improvement in electrocardiogram observed in Case 3 as shown by records made on same day, (A) before and (B) after the removal of 150 cc. of pericardial fluid. Further improvement shown in (C) after 33 days of thyroid medication.

Thyroid treatment was cautiously given to this patient because of the history of angina. On 30 mg. of thyroid daily her metabolic rate remained at -26%, although the cholesterol fell to 176 mg. Nevertheless the electrocardiogram showed increased voltage and T-waves that were more nearly upright and the cardiac

enlargement of the heart shadow. In each the exhibition of thyroid resulted in a regression of the effusion. In other words, the effusion played both a constant and a considerable role in the cardiac findings and was related

directly to the myxedema. In Case 1 this relationship was demonstrated 3 times.

We also believe that the *electrocardiographic changes* noted in myxedema heart by many observers may largely, if not wholly, be caused by the fluid in the pericardial sac. The degree of change under treatment has suggested to others that absorption of fluid seemed at least partly responsible for the improvement noted in the tracings. Moreover the ability to reproduce these changes makes the effusion a more likely explanation than purely myocardial changes. Figure 5 shows two such observations in our Case 1. Nevertheless, myocardial edema might still be present together with the effusion and so could be responsible for some of the changes before, as compared with after treatment.

Therefore, we call particular attention to this observation on Case 3: the improvement in electrocardiograms made on the same day, just before and just after the removal of 150 cc. of pericardial effusion (Fig. 6). This degree of change would occur only after at least 10 days of thyroid administration. Moreover, it is clear, on study of the films of the other 3 cases that some fluid must have remained in this case too, the removal of which would have effected an even closer approach to the final normal tracing at the end of thyroid treatment. (This type of electrocardiographic study could not be made in the other 3 cases because in them we were anxious to get contrast pictures of pericardium and fluid by means of air replacing the fluid.)

That fluid could be the main cause of the electrocardiographic changes also has experimental support. Katz, Feil and Scott<sup>16</sup> injected salt solution into the pericardial sac of dogs and found resultant changes in the electrocardiogram, including smaller Q-R-S complexes and at times a shortened

S-T segment. Scherf<sup>24</sup> in similar experiments noted that the voltage of recorded waves was reduced by one-half, but returned promptly to normal when the fluid was withdrawn from the pericardium.

Further evidence in favor of the major role of pericardial effusion in "myxedema heart" is furnished by the records of the cases reported by others. Of the 16 patients that were observed clinically, 3 were known to have had their effusions during 4, 5 and 16 years respectively<sup>2,9,20</sup> before the myxedema was recognized; yet all 3 did well under thyroid treatment and were free of cardiac difficulties for one or more years at the time of reporting. Boivin's patient<sup>2</sup> had at least 75 pericardial taps before she received thyroid medication at the age of 64. It is hard to believe that these patients could have had severe myocardial disease or much cardiac dilatation for so long a time and yet do so well under treatment.

Effusions into the serous cavities, including the pericardium, have been observed in experimental myxedema by Tatum<sup>26</sup> in rabbits and by Goldberg<sup>11</sup> in sheep.

Furthermore, there are several good reasons against the view that myocardial disease and cardiac dilatation play the chief role in "myxedema heart":

1. Congestive failure is relatively rare in myxedema, as pointed out by Means.<sup>22</sup> What is more, it is uncommon even in the reported patients with obvious "myxedema heart". This has been well discussed by Waring,<sup>29</sup> who points out that in "myxedema heart" the picture is "adynamic", with lethargy, slow pulse and respirations, sluggish heart action; perhaps dyspnea on exertion, but rarely orthopnea; with infrequent cyanosis, pulmonary or hepatic congestion and with normal venous pressure. In congestive failure, on the other hand, the picture is

"dynamic", with tachycardia, dyspnea, pulmonary and hepatic congestion, increased venous pressure and dependant edema.

2. Pericardial effusion in myxedema does not of itself embarrass the cardiac function to any notable degree. This is due probably to two reasons: the slow development of the effusion and the rather surprising distensibility of the pericardium. These account for the relative lack of any tamponade effect, although in each of our patients the pulse rate was slower 24 hours after tapping (80, 72, 70 and 60 respectively) than it had been before (96, 90, 86, and 80). They also account for the large quantity of effusion that may accumulate without much clinical reaction: in Howard's case<sup>15</sup> at necropsy a normal-sized heart was found in an unsuspected effusion measuring 4000 cc.

3. The blood volume is increased in congestive failure. In myxedema the blood volume is usually decreased. It was diminished in the 3 of our patients so studied.

4. The Q-T interval (electric systole), as Tung<sup>27</sup> has pointed out, is increased in cardiac enlargement without effusion; it is normal or diminished in pericardial effusion. It was normal or diminished in our 4 patients.

NATURE OF THE PERICARDIAL EFFUSION. In each of our patients the pericardial punctate had a fairly similar composition. While detailed analyses will be published elsewhere, these salient points are here noted: Each fluid was straw-colored and nearly clear. The specific gravities ranged from 1012 to 1025. The electrolytes (sodium, potassium) were present in about the same concentrations as in the blood. Cholesterol was present in the fluids, but in not over 20% of the amounts observed in the blood (e.g., Case 1: serum cholesterol 650 mg. per 100 cc., punctate 136 mg.; Case 2: serum 608

mg., punctate 76 mg.; Case 3: serum 460 mg., punctate 90 mg.). The total protein figures for punctates were also somewhat lower than for the blood (e.g., Case 1: Serum total protein 7.5 gm., albumin 4.7 gm., globulin 2.8 gm.; punctate total protein 5.9 gm., albumin 4.4 gm., globulin 1.5 gm.). The globulin fraction was relatively lower in punctate than in serum, the extreme figures being in Case 4: serum protein 6.4 gm., albumin 4.0 gm., globulin 2.4 gm., punctate protein 2.8 gm., albumin 2.5 gm., globulin 0.3 gm.

The cellular elements were leukocytes that in total numbers ranged as high as 488 per c. mm., of which 23% were neutrophils and 77% lymphocytes. There were no erythrocytes. The fluids were all sterile on culture, including special studies for tubercle bacilli.

MECHANISM OF PERICARDIAL EFFUSION IN MYXEDEMA. We have no explanation for the occurrence of the effusion into the pericardium or the other serous cavities. We wish, however, to endorse the view of Means and his colleagues<sup>19</sup> that "Myxedema heart" is not a disease of the heart but a manifestation of the disease myxedema. Myxedema heart, and especially massive pericardial effusion which we believe is its major component, appears to be a function of virtual athyrosis, for the fluid clears up on thyroid medication before the metabolic rate has returned to normal. This is a fortunate circumstance, for thyroid medication in myxedema must be used cautiously in all cases. As Christian<sup>7</sup> and others have pointed out, the uncontrolled use of such treatment may have serious and even fatal consequences. Especially in the presence of anginal symptoms is such caution necessary, but even they do not flatly contraindicate treatment, since angina in the myxedematous is at times even helped by thyroid medication.

**THE DIAGNOSIS OF PERICARDIAL EFFUSION.** Our observations emphasize the fallibility of the roentgenological method in the diagnosis of pericardial effusions, even when they are of considerable size. A glance at the illustrations for our cases will show the uselessness of a sign that continues to be mentioned both in roentgenological and physical diagnosis as indicative of effusion: the obliteration of the acute reentering cardio-hepatic angle. Much more significant are the feeble sluggish movements of the shadow on fluoroscopy, the diminished heart sounds and the obliterated or feeble apex impulse with a widened precordial dulness on physical examination and possibly the added help from the electrocardiogram. Perhaps the roentgenologist should acknowledge his limitations by speaking of the "pericardial" rather than the "cardiac" silhouette.

**Summary and Conclusions.** 1. "Myxedema heart" is of not uncommon occurrence in untreated myxedema and has heretofore been explained on the basis of a uniform dilatation of all cardiac chambers. Little consideration has been given to pericardial effusion, a condition reported to date in only 21 cases of myxedema.

2. Yet in 4 consecutive patients with myxedema we have demonstrated considerable pericardial effusion, even when roentgenologic findings were not suggestive of its presence, and in the

absence of any evidence of congestive failure.

3. In all 4 patients the effusion cleared up under thyroid medication, and in one patient this phenomenon was observed in 2 additional periods of hypothyroidism induced with the patient's consent by omitting treatment.

4. The electrocardiographic picture of "myxedema heart", hitherto ascribed to myocardial changes and to the effects of tissue edema, can even better be explained by the effect of a blanketing pericardial effusion. This view is not only suggested by the previous experimental evidence of others, but is strongly supported by our findings of marked electrocardiographic improvement between 2 tracings taken on the same day just before and just after the aspiration of the pericardial effusion.

5. We therefore believe that pericardial effusion is a constant, an early, and the major factor in the cardiac findings in myxedema ("myxedema heart").

6. "Myxedema heart" is not a cardiac disease, but a manifestation of the disease myxedema, and has the much more favorable therapeutic and prognostic outlook of the latter.

7. The nature of the pericardial effusion is described.

8. The diagnostic criteria of pericardial effusion and the limitations of its roentgenologic recognition are briefly discussed.

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## SOME CARDIOLOGICAL PROBLEMS OF THE TROPICS

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IN the 1930-1931 Report of the former "Junta de Caridad de San José", Rotter<sup>30</sup> gives a frequency of 6% of affections of the circulatory system as cause of death among 559 autopsies carried on at this hospital. We have now analyzed 8000 autopsies as a basis for this study, finding a cardiovascular mortality of 768 cases (9.6%). In almost every country there has been noticed in the last decades a tendency toward greater mortality due to such cause, and Costa Rica is no exception to the rule. The quinquennial mortality rate from 1916 to 1940 has climbed from 84.7 per 100,000 inhabitants to 122.3. Already it has been said that in our country the affections of the circulatory system occupy the first place among the causes of death in the population, if those under 5 years are excluded.<sup>23</sup> Moreover, the effect of the tropical location of the country provides distinguishing features of cardiological practice in this country, as we have been able to ascertain after more than 10 years' experience.

The climate has a favorable influence upon the rarity of cardiac complications in goiter. Classical exophthalmic goiter prevails in regions that have a continental climate, but not in those of a maritime climate, such as exists in our country. On the other hand, the same as in the mountainous countries of Europe, endemic goiter is not at all rare, it being known that the inhabitants of the high valleys are predisposed to suffer from it.

It is also probable that climatic factors are related to the rarity of bacterial endocarditis, either by modifying the microorganism's virulence or enhancing

the host's resistance. The local frequency of parasitism and the carelessness of the inhabitants open wide doors to infections such as pyodermatitis and oral sepsis. By such means perhaps the immunity to the microbes commonly causing the bacterial endocarditis is increased.

The climate, on the contrary, is unfavorable in its effect upon faulty nutrition, either through economic factors affecting the consumer or by directly modifying a subtle nutritional equilibrium in foods. The relative shortage or the high price of fats and its lesser consumption due to the warm climate probably is a factor in the rarity of myocardial infarction (in hospital patients), influencing in a favorable sense the evolution of coronary arteriosclerosis.

It is recognized that among the diverse causes of heart disease parasites hold a place. Precisely the tropical climate creates adequate conditions for the transmission of malaria, Chagas' disease, ankylostomiasis, to mention just a few tropical affections which might be accompanied by cardiac disturbances.

The following points deserve special comment: 1. Medical geography; 2. The frequent causes of heart disease; 3. The rarer causes of heart disease; 4. The heart in relation to some tropical diseases.

1. MEDICAL GEOGRAPHY. The territory of Costa Rica is subject to 3 geographical factors—latitude, altitude and the two oceans—which affect its climatology materially.

This country is very near the equator; the capital, almost in the center of

the country, is situated approximately at 10° northern latitude. Therefore it must be classified as located in the inter-tropical zone. The low regions are formed by plains and virgin forest, but soon the mountainous spurs begin and reach above 12,000 feet at their highest altitude. Two parallel ranges divide the country into two watersheds which flow into the Caribbean Sea on the East and the Pacific Ocean on the West. The width of the country varies from 70 to some 170 miles. The mountains run from northwest to southeast. Two large rivers surround the central plateau that shelters the greatest part of the population, its climate being better fitted for the development of human activities. These data will help to explain the climate in relation to atmospheric temperature, barometric pressure, evaporation, sunshine, humidity, clouds, wind and rain.<sup>35</sup>

1. *Air Temperature.* Hot on the coasts as expected at this latitude, it is refreshed by sea breezes, not yet well studied. The temperature is highest in the low regions in which the sea influence is small, and starts to fall with altitude. The territorial block, for reasons stated, is not subject to the sudden variations of temperature of those regions more distant from the equator and properly continental.

2. *Barometric Pressure.* Pressure diminishes with elevation but it remains very stable because of the absence of the disturbances of the continental masses.

3. *Evaporation, sunshine, humidity.* These factors are greatly influenced by latitude. It has been rightly said that a tropical sun is always a tropical sun. The altitude is of little influence apparently, although we have no definite figures on this matter.

4. *Clouds.* Generally the sky is clear in the morning, but soon becomes cloudy with an excessive evaporation.

5. *Winds.* The changes of the air

masses between the hot ground and the upper atmospheric layers and the influence of the slopes of the mountains foster winds on the plateau, not thoroughly known, which appear to be an important factor in the local variations of the climate. On the other hand, trade winds blow continually from the northeast, laden with the oceanic refreshing humidity. Winds from the south blow at different periods; their influence is not clear.

6. *Rain.* The direction of the mountain range, perpendicular to that of the northeastern winds, remarkably influences the quantity of water which is precipitated on the Caribbean watershed, where the rainy season is practically continuous. The precipitation on the rest of the country obeys a more obvious rhythm, the rainy months are from May to November and the dry season follows during the balance of the year. The type of rain is that brought by the northeastern winds: brief, abundant, stormy.

In short, we can say that although Costa Rica is placed among the regions of hot climate, it offers, depending on the watershed, either the type of equatorial climate without any true dry season, the biological characteristics of which include among others richness of vegetation and intense parasitism; or the type of tropical climate with a dry summer and a rainy season in the winter. Besides, the central plateau enjoys the characteristics of the mountain climate of the hot regions: little temperature variations (average 68° F.), absence of a stimulating rhythm with that sweetness of the perpetual Spring which conceals the somnolence of the mind and of the senses.

The altitude of the plateau varies between 3,000 and 8,000 feet. However, the view that this elevation above sea level may constitute an unfavorable factor for the circulatory system is not supported by clinical observation. Peo-

ple adapted to the plateau are seen to be clearly differentiated in their vascular reactions from subjects who have been suddenly transported to considerable heights or who are submitted to barometric variations in air chambers.

2. THE FREQUENT CAUSES OF HEART DISEASE. The fundamental causes of heart disease can be summarized into 4 etiological groups: sclerosis, rheumatism, syphilis and cardio-pulmonary. These comprise almost 90% of the types found post-mortem. In the sclerosis group we include calcific aortic stenosis, aortic atheroma, generalized arteriosclerosis, coronary arteriosclerosis, myocardial infarction and generally the so-called cardio-renal group. In the rheumatic group are included all valvular lesions except the syphilitic and cal-

South of the United States, in a comparable group of 8313 autopsies found 117 cases whose death was due to myocardial infarction and, or, coronary occlusion (an incidence of 1.4%).

We may safely conclude that coronary artery disease and acute coronary thrombosis do not have among hospital patients an importance comparable to that of northern countries. It is possible, of course, that the important factor to which this phenomenon might be due is a diet poor in fats, related to adverse economic factors affecting the population served by hospitals, and to the lessened caloric requirement in a mild climate.

Contrary to what has been declared by authors without tropical cardiologic experience, rheumatic heart disease

TABLE 1.—FREQUENT CAUSES OF CARDIAC DEATHS IN COSTA RICA

Etiology	% of all Autopsies	% of Cardiac Deaths	Females	Males
Sclerosis	4.4	46.1	118	238
Rheumatism	1.7	18.0	53	86
Rheumatism & Calcific Aortic Stenosis	1.9	20.0	59	100
Syphilis	1.8	19.1	27	120
Cardio-Pulmonary	0.4	5.0	16	23
			<hr/> 273	<hr/> 567

cific aortic stenosis. But due to etiologic doubts<sup>19</sup> concerning aortic stenosis with calcification of the valves, we have made a sub-group of these cases plus those properly rheumatic. In the syphilitic group are included syphilitic aortitis and aortic aneurysm. In the cardio-pulmonary group are classified heart failure secondary to a pulmonary disease, bronchiectasis in most of the cases.

In Table 1 we present data gathered in our study of 8000 necropsies.

We have been much impressed by the few cases that were found of myocardial infarction, only 23 (0.2%) of the total number of autopsies. Master<sup>24</sup> concludes that in the United States 114,000 persons die annually from coronary artery disease. Holoubek<sup>16</sup> in the

is fairly frequent. It seems to us unquestionable that bad hygienic living conditions of a great sector of the population determine its incidence. Holoubek's<sup>16</sup> figures are less than our own, 15.6%. The same is true of Scott and Garvin's<sup>32</sup> in Ohio. Clawson<sup>5</sup> in Minnesota, among 30,265 autopsies finds 18.6%. Additional studies on this subject have been published elsewhere.<sup>9</sup> We can conclude by saying that climate by itself does not possess preventive or curative virtues for rheumatic cardiopathies.

The frequency of syphilis might seem relatively high. However, it is less than that found in other countries of similar racial and social characteristics.<sup>11</sup> For instance in Puerto Rico, Koppisch<sup>21</sup> reviewed 1259 autopsies, finding an in-

cidence of 10% of all forms of heart disease, of which syphilis was the most important cause, being found in 30% of the cardiac cases. Among our people a high percentage of negro patients who died from this cause is observed. The incidence of negroes with syphilitic heart disease is 31.9%, much higher than in any other form, the percentage of negroes among the total cardiovascular mortality being only 17.5%. Excluding this race, the incidence of cardiovascular syphilis is reduced to 13%.

3. THE RARER CAUSES OF HEART DISEASE. These less frequent causes of heart disease represent 11.4% of the

implications.<sup>14</sup> One may conclude that the so-called isolated myocarditis (Fiedler's) is not the best inclusive term for such a heterogeneous group of diseases. A new approach toward the possibility of myocardial damage produced by allergic and metabolic disturbances, including malnutrition, is evident. The cases associated with hepatic cirrhosis seem to us<sup>10</sup> particularly revealing in view of the fact that cirrhosis has been mentioned as associated with beri-beri heart disease in alcoholics. Besides, there has been recently much insistence upon deficiency factors in the etiology of cirrhosis of

TABLE 2.—RARER CAUSES OF HEART DISEASE IN COSTA RICA

Groups	Etiology	Cases
1. Lack of Data	Unknown	13
2. Rare Types	Myocardial Abscess	1
	Cysticercosis of the Myocardium	1
	Necrotic Post-partum Myocarditis <sup>15</sup>	1
	Pericarditis	7
	Rupture of the Aorta	1
	Tumor of the Heart	2
3. Rare Types in Other Countries	Anemia	18
	Ankylostomiasis	10
	Ankylostomiasis & Nephrosis	1
	Malnutrition & Hepatic Cirrhosis	5
	Malnutrition & Tuberculosis	4
4. Frequent Types in Other Countries	Congenital Heart Disease	7
	Fatty Infiltration of the Heart	1
	Bacterial Endocarditis	21
Total		93*

\* 6 cases duplicated in Table 1.

total cardiovascular mortality reviewed. Excluding those affections rare by themselves and the uncertain cases due to lack of data in the autopsies and clinical study, 2 important sub-groups remain. The first is that of causes rarer in other countries, chiefly anemic and nutritional heart disease. The second is that of causes more frequent in other places, especially sub-acute bacterial endocarditis (See Table 2).

A review of recent studies made on myocardial syndromes of uncertain etiology reveals that authors do not agree on terminology or pathogenic

the liver. Clinically these cases can be diagnosed as myocardial fibrosis, as the autopsy findings show zones of fibrosis in the myocardium and endocardium with parietal thrombus formation and frequently far reaching embolization.<sup>9,33</sup> Although our study has been made among subjects living in conditions of relative malnutrition it is surprising that the number of cases is not higher. It is possible that many such patients who die of intercurrent diseases are classified under tuberculosis, pneumonia, and so on.

More frequently we observe clini-

cally and in the necropsies anemic heart disease due to the high incidence of ankylostomiasis. We shall refer to this affection later.

It is known that bacterial endocarditis in its acute form is usually very rare. In our material we found only 2 such cases. As it may appear in the course of many infectious diseases and this particular group of cases was not surveyed, our statistics are incomplete, so we shall take under consideration only 19 cases of the subacute variety.

P. D. White<sup>37</sup> says that subacute bacterial endocarditis occurs in about 5% of cases of rheumatic heart disease and he supposes "that in communities where rheumatic heart disease is infrequent the predisposing factor of con-

We believe that, contrary to current medical thinking,<sup>29</sup> the presence and persistence of known focal infection in rheumatics in some way protects them from bacterial endocarditis. It is only among those rheumatics who take excessive care of themselves by eradicating all possible foci of infection, or who by chance come in contact with more virulent organisms, that a secondary bacterial endocarditis is likely to develop. It is a fact that the rheumatics we meet every day in hospital practice never bother about prophylaxis. And the same is probably true regarding the poor population of the Southern United States or the tropical workers in the Panama Canal Zone (See Table 3).

TABLE 3.—DEATHS FROM RHEUMATIC HEART DISEASE AND BACTERIAL ENDOCARDITIS IN NORTH AND CENTRAL AMERICA

Authors	Cardiac Deaths	% Rheumatism	% Bacterial Endocarditis
Clawson, Minnesota	4678	18.6	11.0
García Carrillo, Costa Rica	768	20.0	2.7
Holoubek, Louisiana	1045	15.6	4.7
Kean, Canal Zone, Panamá	2497	—	2.8
Scott & Garvin, Ohio	790	15.1	5.6

genital defects is as important as is that of rheumatic valvular disease, and in such communities one would expect to find the total incidence of subacute bacterial endocarditis considerably reduced in comparison with that in rheumatic areas". Among our cases, on the contrary, there stands out only one case of endocarditis upon a congenital lesion opposing the total cases of rheumatic heart disease. Our incidence of subacute bacterial endocarditis is 2.7%. Holoubek<sup>16</sup> gives a figure of 4.7%. Kean,<sup>20</sup> analyzing 14,304 autopsies among workers in the Canal Zone, Panama, gives figures like ours: 2.8% (when Americans are included: 3.7%).

In Holoubek's<sup>16</sup> statistics approximately half were negroes; in Kean's<sup>20</sup> series 63.3% of the total were negroes. In ours there was only one doubtful case, so we minimize the racial factor.

We recall that Libman and Friedberg<sup>22</sup> deal with the immunization problem as follows: "A trial of prophylactic immunization of patients with acquired valvular and congenital heart disease seems indicated since the usual causative organisms in the persons affected are known. The difficulty lies in the absence of immunologic tests to determine whether any immunity has been effected".

To close this section let us point out that significant fatty change of the myocardium is an exception, only 1 such case being found in our material.

4. THE HEART IN RELATION TO SOME TROPICAL DISEASES. We do not find in this series of autopsies any case of myocarditis due to Chagas' disease or to malaria. But as no special research was done in malaria it can not be ascertained what was the incidence of myo-

carditis or what may be its relation to anemic heart disease.

There is no evidence in favor of valvular lesions being produced by malaria, but in certain cases of the so-called pernicious attack, sudden death may occur. Generally it happens to be a paludic case with high fever, pallor or cyanosis, dyspnea, profuse sweating, delirium, precordial anguish or pain, rapid, irregular and small pulse, weak heart sounds, arterial hypotension. On necropsy the heart capillaries have been found full of malarial parasites.<sup>18</sup>

In advanced cases of malaria or ankylostomiasis heart failure can result, as has been observed by many authors with experience in severe anemias. In such cases the red blood cells amount only to 1 or 2 millions, sometimes around 500,000 per cu. mm. The hemoglobin is commonly only 30 or even 10% of the normal. The heart is enlarged and a gallop rhythm is present; apical systolic murmurs are frequent and even aortic diastolic murmurs can be heard.

The pathologic anatomy of the heart in fatal ankylostomiasis has been described by Calmette and Breton<sup>2</sup> as follows: "Within the pericardial cavity an abnormal quantity of fluid, sometimes slightly hemorrhagic, is found. The heart is flaccid, dilated, the walls of the ventricles are thin and show fatty degeneration. The right cavities as well as the left in certain cases, are full of fibrinous clots. Occasionally clots are also found in the cranial sinuses." We believe that the tendency towards thrombosis that has been observed<sup>31</sup> among ankylostomiaties is due at least to a great extent to relative immobility. Sudden death due to massive pulmonary embolism, or to several small emboli followed by pleuro-pulmonary complications is not infrequent.<sup>12</sup> It seems quite possible that they impose a burden on a heart already strained by the anemia and

nutritional deficiencies. The often fatal cardio-pulmonary syndrome of the ankylostomiatie can thus be integrated. Its prophylactic treatment, by correcting incipient heart failure and prescribing slight exercise, might decrease somewhat the high mortality due to hookworm infection in the tropics.

Chagas' disease<sup>8</sup> generally starts by the sting of an insect of the *Triatoma* species, especially in the face, or by contamination with its excreta which introduces the trypanosomes into the circulation. The initial sign is cutaneous, frequently a unilateral palpebral edema with dacryoadenitis and secondary adenopathy called the ophthalmoganglionic complex, which nevertheless is not pathognomonic. The cardiac evolution of the acute cases is manifested above all by a sinus tachycardia not related to the temperature, generally moderate and unstable, with a certain predilection for occasional premature contractions. In some cases the radiography reveals a slight or moderate increase of the cardiac silhouette. The electrocardiogram shows changes in the shape of the waves, especially the T wave and the ST segment. The anatomo-pathological study of the heart shows intense proliferation of histiocytes, infiltration of leukocytes and lesions of the muscular fibers, atrophy or fatty degeneration. The trypanosome, in the form of leishmania, can be seen in the myocardium. Lesions of the valvular endocardium are not known to exist.

This trypanosomiasis has been described in Costa Rica since 1941<sup>30</sup> and several cases have been well studied.<sup>3</sup> When the disease enters a chronic stage due to reinfection or to evolution of the organisms inside the body, a chronic cardiopathy can conceivably exist; but we have no experience on such cases. Usually it is the picture of myocardial fibrosis, the etiological diagnosis of which is based upon a specific

complement fixation reaction. Neither do we have experience with other diseases which may be seen in the tropics and be complicated by myocarditis, such as typhus fever, yellow fever, echinococcus disease, infestation with other parasites and so on.

To the observer in the tropics, the accidents produced by the bites of venomous snakes are impressive and well described in medical literature.<sup>1,25,27</sup> Well known are the weakness of the heart during the envenimation and the production of cardiac lesions.<sup>26</sup> As it seems that serial electrocardiography has not been carried out in the course of such poisoning, we shall now speak of our opportunity to study 11 subjects on whom 25 electrocardiograms were taken.

Our snakes belong to the *Bothrops* species, which predominate in Central and South America.<sup>28</sup> Statistics<sup>4</sup> show that some 23 snake bites per 100,000 inhabitants happen annually in Central America. In 8,000 autopsies which we surveyed only 10 cases were found of death due to snake bite, and the snakes involved were practically always *Bothrops atrox* or *Bothrops schlegelii*. The most important finding in these patients consists of multiple hemorrhages. In the cases reported by us<sup>13</sup> these occurred frequently in the gastrointestinal tract and in the brain as well as in the renal pelvis. In one patient, aged 67, a cardiac dilatation was noted, but the most common lesions in the heart were sub-endocardial and sub-epicardial petechial hemorrhages which were prominent in 3 cases. Pulmonary congestion and edema were mentioned in 5 autopsies.

Cardiac alterations would be due to the action of cytolytins,<sup>27</sup> but the heart is also affected by disturbance of its nervous equilibrium or of its internal medium (homeostasis), effects which are not infrequent in the complex action of venoms. Houssay and

Mazzocco<sup>17</sup> showed that muscle treated by dilutions of snake poison has an abnormal permeability characterized by loss of certain elements such as phosphorus and, even more, potassium. This liberation of potassium recalls that of hemoglobin; that is, there is analogy between the action on the muscle and the hemolysis of red cells. This parallelism is interesting in considering the interpretation of the electrocardiogram, because today we know that this record in man can be modified in accord with the level of potassemia.

From the evidence gathered,<sup>13</sup> it can be concluded that in cases of snake bite associated with toxic phenomena the electrocardiographic pattern is the same in every case and consists of T waves of relative low amplitude and rounded apex, in one or more leads, and slight depression of the ST junction in precordial lead CR5 with prolonged QT. When the snake bite is not followed by toxic symptoms, these modifications are non-existent or very slight but of the same nature.

**Summary.** This article deals with a study of cardio-vascular disease made in the Republic of Costa Rica, based upon the analysis of 8,000 autopsies.

A mortality rate of 9.6% attributable to this cause was found. The sclerotic form of heart disease, including the so-called cardio-renals, amounted to 46.1% of the cardio-vascular deaths. Rheumatic heart disease contributed 20%, including aortic valve calcific disease. Syphilitic heart disease gave a rate of 19.1% when negroes are included, and only 13%, excluding this race. Cardio-pulmonary heart disease amounted to 5.0%. In the group of rarer causes are mentioned affections due to malnutrition, ankylostomiasis and snake venoms.

We stress the rarity of myocardial infarct (0.2% of the total autopsies) and of sub-acute bacterial endocarditis. In explanation, factors of nutrition and



the mode of living of those people who attend hospitals are pointed out.

The climate of the tropics influences certain aspects of cardiological practice. To bring this out, reference is made to the climatology of Costa Rica and the relation of climate to parasitic diseases affecting the heart, in particular malaria, ankylostomiasis and Chagas' disease. In regard to ankylostomiasis we define the cardio-pulmonary syndrome which marks in some cases the

end of this helminthiasis.

The effect of poisonous snake bite on serial electrocardiograms was studied. In the most serious cases a pattern which consists of T waves of relative low amplitude and rounded apex in one or more leads with a slight depression of the ST junction in precordial Lead CR5 and prolonged QT interval was discovered. It is suggested that these anomalies might be due to hypopotassemia.

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# THIOUREA COMPARED WITH PROPYLTHIOURACIL IN THE TREATMENT OF THYROTOXICOSIS

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ALTHOUGH thiourea was one of the first anti-thyroid drugs employed clinically, it was soon superseded by other compounds. Its early decline in popularity may be attributed both to its supposed low potency as indicated by animal assay, along with a high incidence of side reactions in the dosage originally employed (1 to 2 gm. daily).

The data, herein presented, were accumulated in order to compare the clinical usefulness of thiourea in small doses with that of propylthiouracil.

Patients consisted both of staff cases and private patients followed by members of the staff. In keeping with the practice of Danowski, iodine was given along with the thiourea in almost all

TABLE 1.—THERAPEUTIC RESULTS

	Average daily dose (grams)	Average time for complete control (weeks) <sup>o</sup>	Patients requiring greater dose for control†	Number showing overdosage effects	Number of cases receiving this dose anytime
Propylthiouracil (38 cases)	0.1	5.0 (7)	19% (7)	0	19
	0.2	3.7 (14)	8% (3)	0	22
	0.3	4.0 (2)	3% (1)	0	4
Thiourea (41 cases)	0.1	10.0 (1)	12% (5)	2	10
	0.2	4.7 (8)	5% (2)	2	20
	0.3	5.5 (24)	0 (0)	1	27

<sup>o</sup> This average was obtained only from those patients who responded to an initial dose of the stated magnitude. The number of cases is in parenthesis.

† Percentages are in terms of total series. These patients were evaluated 3 to 8 months after initiation of the stated dose. Also are included those who relapsed when previous higher doses were reduced to this level. In parenthesis are number of cases not controlled at this dose.

Danowski and co-workers, however, have found the compound to be a very effective and non-toxic drug when given in doses of 0.025 to 0.3 gm. daily.<sup>4,5,10</sup> Moreover, Astwood has recently shown that in the human subject thiourea is actually somewhat more potent than propylthiouracil in its capacity to inhibit the synthesis of thyroid hormone.<sup>13</sup>

instances (15 min. Lugol's sol. daily). A minority of patients on propylthiouracil received iodine. It is the contention of Danowski's group that iodine enhances the therapeutic response of the drug. Others believe that there is a slight impairment in rate of improvement,<sup>7</sup> or no significant difference.<sup>8</sup> The present study does not provide evi-

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dence on this point, except that iodine most certainly did not prevent a positive response to either drug.

**Efficacy of the Drugs.** Table 1 summarizes the therapeutic results. No patients were included in this tabulation who did not have perfectly typical hyperthyroidism, or who were not followed carefully enough to assess therapy. Complete control is defined as restitution of metabolic rate and pulse to normal, along with distinct weight gain and subsidence of subjective symptoms.

The data suggest that a dose of 0.2 or 0.3 gm. daily of either drug results in more rapid improvement than 0.1 gm. There is no doubt, however, that thiourea is effective in doses as low as 0.1 gm. daily. This dose in some in-

patient getting 0.2 gm. propylthiouracil and one on 0.3 gm. thiourea plus Lugol's showed a distinct increase in the size of the thyroid, and the gland also became softer in consistency. In the latter instance, the enlargement was 2 or 3 fold and a bruit appeared. Regression followed cessation of treatment. The remaining patients of the combined series showed no apparent changes in the gross size of the thyroid.

Exophthalmos, if present, was measured in most instances and was not consistently altered to any great extent in either direction by treatment.

**Toxicity.** In Table 2 "proved reaction" denotes that reduplication of the effect was readily obtained by readministration of the drug. A "possible reaction" is one which occurred

TABLE 2.—NUMBER OF CASES SHOWING TOXIC REACTIONS

		Nausea	Fever	Rash	Leukopenia	Agranulocytosis	Total Cases
Propylthiouracil (51 cases)	Proved	0	1	0	0	0	1
	Possible	1	0	0	1	0	2
Thiourea (49 cases)	Proved	1	3*	1*	0	0	4
	Possible	2	1	1	0	0	4

\* One case had both fever and rash.

stances is actually too high for continual maintenance. The figures on overdosage are not susceptible to statistical comparison because one always attempts to forestall overdosage by reduction of intake to the minimum which is required. One patient was not completely controlled on 0.3 gm. propylthiouracil and, in general, the dose required for complete control averaged somewhat higher than with thiourea. It will not be justified, with the data at hand, to attempt any precise comparison of potencies of the 2 drugs; however, it is fair to conclude that their clinical efficacy is of similar magnitude.

In 4 cases receiving 0.1 gm. to 0.2 gm. propylthiouracil and 2 cases receiving 0.2 to 0.3 gm. thiourea plus Lugol's solution, the gland became slightly but measurably smaller, but one

during treatment and promptly disappeared upon withdrawal of the drug, but following which no subsequent test dose was given. Neither drug produced agranulocytosis or any other dangerous complication. Side effects, such as fever, rash, and nausea were considerably more common with thiourea. Three instances of proved fever due to the latter drug (0.3 gm. daily) occurred after 10, 14, and 14 days respectively. The case of fever classed as "possible" was encountered after 9 days on this same dose and the "possible" rash occurred after a similar interval on 0.2 gm. daily. Nausea, which was seen mainly with thiourea (0.2 to 0.3 gm.) appeared immediately after treatment was started and necessitated discontinuance of the drug.

It should be mentioned that 2 of the

patients who had received thiourea (0.2 gm.) and iodine for several months developed unexplained fever, swollen, painful joints, and myalgia which persisted for 14 to 21 days after the drug was stopped, but no fever could be induced later by test doses of either the drug or iodine. Another patient showed non-thrombocytopenic purpura, which was not affected by discontinuance or resumption of 0.2 gm. daily at intervals of several weeks. The drug was then discontinued, however, and eventually the purpura cleared with no recurrence after more than a year. It is impossible to say whether these 3 cases represent unusual toxic reactions.

The single febrile episode due to pro-

rate of 77%. The 6 cases which did not relapse have been followed from 6 months to over 3 years. One does not find in the present data any correlation of relapse rate with age, size of gland, duration of treatment, severity of disease, or the type of gland (Table 3). The suggestion of less frequent relapse in cases of short duration is not statistically significant. In addition to a comparison of averages as recorded other statistical evaluation likewise showed no positive relationships. When relapse occurred it was clearly evident within an interval of 2 to 8 weeks.

**Preparation for Surgery.** Twenty-three patients were operated on after being treated with drug. Fifteen were

TABLE 3.—ANALYSIS OF REMISSION AND RELAPSE

	AVERAGES	
	Pts. relapsing	Pts. not relapsing
Age	49	42
Size of Gland	"1.8 plus"	"1.6 plus"
Duration Disease	9 mo. $\pm$ 1.2°	6 mo. $\pm$ 1.3°
Duration Treatment	8 mo.	9 mo.
Percent of group with nodular gland	35%	33%
Percentage distribution	Mild	17%
according to severity	Moderate	33%
of disease	Fairly Severe	33%
	Severe	17%

° St.E.—Standard Error

pylthiouracil appeared after 9 months of medication (0.1 gm. daily). Fever was reproduced on 4 subsequent occasions by 50 mg. of the drug. The case of leukopenia is classed as a possible reaction because of a white count of 3600, polymorphonuclear leukocytes 33%, anorexia, dizziness, and headache 15 days after 100 mg. daily was started. All findings were normal 2 days after stopping the drug. The instance of nausea with propylthiouracil occurred immediately after starting 0.2 daily on two occasions. One tenth gram daily was tolerated with very little nausea.

**Relapse After Discontinuance of Drug.** Of 27 cases controlled by drug for 3 months to 2 years and later withheld from treatment, 21 relapsed, a

judged to be completely controlled preoperatively, and this group had a post-operative course which was considered very smooth in every case. The remaining 8 patients were not brought under complete control before operation. Four experienced a rise in temperature and pulse judged to be excessive. Two of these were treated as mild storm and recovered. A third did not have a thyroidectomy, but died in typical storm after hysterectomy. She is included to illustrate the hazard of storm after the stress of surgery in incompletely controlled patients. It is clear from these experiences that there is no magic in preoperative preparation with anti-thyroid drugs unless adequate doses are

given for sufficient time to insure complete remission.

Table 4 summarizes difficulties encountered with excessive bleeding and friability at operation, along with an appraisal of the histological state as judged by the pathologist. As would be expected, iodine given with or after the drug reduced the incidence of excessive hyperplasia, although involution has frequently been incomplete. It may be noted that in 10 cases receiving iodine alone, which are included for comparison, involution, even here was by no means complete. In general, the histological state of the gland after iodine plus drug was not materially different from that after iodine alone.

**Comments.** The above observations confirm the effectiveness of thiourea in

inferior to propylthiouracil in its higher incidence of side reactions, although major complications, such as agranulocytosis, have not as yet been met with during use of thiourea.

The reported frequency of relapse after termination of drug therapy varies from 33 to 62%.<sup>2,6,8,15</sup> The over-all average in 225 reported cases, including the present series, is 55%. The present data do not bear out the impressions of others that relapse is less frequent in the presence of a small gland or in mild cases of the disease.<sup>2,12,15</sup>

**Summary.** 1. Most patients given thiourea were controlled by doses of 0.1 to 0.3 daily. Side reactions, chiefly fever, occurred in 16% of cases; no dangerous toxicity was encountered.

2. In 51 cases treated with propylthiouracil there was 1 instance of fever,

TABLE 4.—ANATOMICAL CONDITION OF THYROID GLAND  
NUMBER OF CASES

	Total	Technical operative difficulty	Gland predominantly hyperplastic	Evenly mixed hyperplasia & involution	Predominantly involution
Drug alone	7	4	4	1	2
Drug plus iodine or followed by iodine	15	1	4	5	6
Iodine alone	10	1	3	3	4

low dosage. The incidence of side reactions was, however, higher than reported by the New Haven group who encountered only 2 cases of fever in 120 treated cases.<sup>5</sup> The low toxicity of propylthiouracil is in agreement with the experience of others.<sup>1,3,6-11,14</sup> The present series, combined with cases obtained from the literature, gives an over-all incidence of proved or suspected side reactions of 270 in 960 cases, and only one case of agranulocytosis was seen in the combined series. It may be concluded that thiourea is

1 of mild leukopenia, and 1 of nausea. Complete control of thyrotoxicosis occasionally required doses in excess of 0.3 gm. daily.

3. Iodine given with an antithyroid drug did not interfere with its efficacy and produced an involution of the gland similar to that seen after iodine alone.

4. Relapse rate in 27 cases after withdrawal of drug was 77%. No factors were discovered which allowed prediction of a sustained remission in a given patient.

We are grateful to those members of the staff who have furnished data on private patients for inclusion in this study. We are also indebted to Dr. Stanton M. Hardy of Lederle Laboratories and Dr. L. E. Josselyn of Abbott Research Laboratories for supplying the propylthiouracil which was used during the early part of the study.

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# CONCENTRATED ROENTGEN THERAPY OF CERVICAL TUBERCULOUS LYMPHADENITIS

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THE roentgen therapy of tuberculous adenopathy, especially the cervical form, is a well established procedure within radiology, although it is somewhat less known as an efficacious treatment in the various branches of the medical profession which are the source of the radiologist's patients. Although reports on the excellent results secured by this form of therapy have appeared periodically in the radiological and other medical literature, the present time seems appropriate to reaffirm several points in connection with the treatment of this disease as well as to present the advantages and results of a concentrated technique of irradiation. The introduction of streptomycin as treatment for tuberculous involvement in various parts of the body raises the question as to the present status of roentgen treatment of tuberculous adenopathy. The purposes of this report are: (1) to re-emphasize the high quality of results secured by roentgen therapy, (2) to point out the advantages in time and convenience of our particular plan of treatment, and (3) to contrast the results of roentgen therapy with streptomycin in the treatment of the tuberculous adenopathy.

Study has been limited to cases of cervical tuberculous lymphadenitis, since this group is numerically large enough to furnish a satisfactory basis for analysis, although tuberculous aden-

itis in other parts of the body, notably the inguinal and axillary areas, is treated by us and known to respond to irradiation. During the period 1939-1947, 42 cases of cervical tuberculous lymphadenitis were accepted for treatment in the Therapy Division of the Department of Roentgenology, University of Michigan Hospital. Of these 42 cases, treatment was completed and follow-up was considered adequate in 37 cases and these form the basis of our study.

Diagnosis was confirmed by pathological or bacteriological material in 30 cases (80% of the series). The remaining 7 cases presented clinically characteristic features of tuberculous adenopathy, 3 having radiographic evidence of active or quiescent pulmonary tuberculosis and 1 having calcium in cervical nodes. Another patient had a life-long history of repeated suppuration and breakdown of cervical lymph nodes and in infancy and childhood drank milk from cows which were later ordered slaughtered because of tuberculous infection. In 2 cases such corroboratory evidence was lacking but the clinical course and response in every way justified the clinical impression. It must be emphasized that bacteriological or pathological proof of the clinical diagnosis should be diligently sought after in every case since confusion with non-specific cervical lymph-

adenitis, various other infections of the cervical nodes, thyroglossal or branchial cleft cysts, lymphoblastoma, or metastatic carcinoma can otherwise easily result.

*Roentgen therapy used.* The technique of treatment in these cases consists in using radiation generated at 200 kilovolts, filtered with 0.5 mm. copper and 1.0 mm. aluminum (half-value layer 0.9 mm. copper) at a target-skin distance of 50 cm. and at a rate of about 50 r per minute. Fields are large enough to include the obviously diseased nodes as well as the regional group and have varied from 8 x 10 cm. up to 15 x 15 cm. Treatment is given daily, 200 r (measured in air) to one field, for 4 or 5 days. In the case of children or debilitated adults 100 to 150 r to one field is given. Usually total dosage is 800 to 1000 r per field and at completion the patient is asked to return in 2 to 3 months. An occasional patient is given a second course at that time. If good regression does not follow the second course, the response is considered unsatisfactory and further irradiation is not given.

The reactions ensuing from this method of irradiation are insignificant. Slight soreness in the throat may appear but is transient. The acute reaction in the skin is essentially negligible. No late cutaneous damage has been seen even when 2 courses were given. Even radiation pigmentation is minimal or, more often, absent.

The experiment of employing a radiation technique concentrated in respect to time as opposed to the traditional protracted method was motivated by the practical inconvenience of the latter and an undesirable incidence of definite (sometimes severe) radiation damage of the skin. Multiple intermittent irradiations over a protracted period may produce significant to severe radiation changes while larger doses (within certain limits) given in a short time and never repeated will result in lesser degrees of permanent tissue change. It is of interest that in the cases reported here there is only one in which evidence exists to suggest suppuration induced by irradiation. In this patient with a small solitary lymph

node of 1 to 2 weeks duration, it was reported to us that the node became fluctuant 1 month after treatment and that aspiration was performed with subsequent regression of the adenopathy. It is an open question whether the suppuration in this case was the result of irradiation or spontaneous. Suppuration did not follow treatment in any of the other patients, many of whom had bulky masses of involved nodes.

Results were classified as satisfactory or unsatisfactory. Intermediate grades of improvement less than complete regression have all been grouped together as unsatisfactory since it was felt that anything less than complete regression is unsatisfactory when dealing with a chronic disease which is subject to regression over a long period of time even when untreated. On this basis of evaluation we have had complete regression in 31 cases (84% of the patients studied). Six patients (16%) were thought to show unsatisfactory response although there was some improvement in several after either one or two courses of treatment. Of the 31 patients showing complete regression, 23 had draining sinuses present at the inception of therapy, some of these sinuses having developed following biopsy or drainage of fluctuant masses. In the 6 cases where response was unsatisfactory, there were 4 with draining sinuses. From this it appears that the presence of draining sinuses has no particularly adverse effect on the results of radiation therapy. Conservative surgical procedures are advantageously combined with irradiation. Fluctuant masses on the verge of breakdown may be aspirated, if possible, or incised for diagnostic or therapeutic reasons. Radical neck gland dissections should play no part in the modern management of tuberculous adenopathy and can usually be avoided.<sup>3</sup>

Examination of our data shows that



there was a wide range of duration of the nodes prior to roentgen therapy, from several weeks to many years. In the 31 cases with satisfactory results, in about 26% the adenopathy had been present for 6 weeks or less, compared to approximately 40% in the small group of 6 cases with poor response to treatment. For the first group, 52% had nodes for 6 months or less, and 71% for 1 year or less; the respective figures for the second group are 60% and 66%. The differences of duration prior to treatment, in those cases responding well to irradiation and those that did not, cannot be deemed significant.

It is difficult to estimate the time in which regression of the diseased lymph nodes takes place. Because they have no further trouble, many patients do not return at the requested interval of 2 months. Some are seen only at later dates because other clinics in the hospital to which the patient applies for treatment of unrelated conditions months or years later refer them to us. Often a statement in the patient's record to the effect that no evidence of cervical adenopathy is found at the present date must be interpreted as complete regression but gives no indication of the time of clearing in relation to the treatment. Conversely, the patients with incomplete regression are those who are likely to return at the specified intervals for check-up. One can therefore only form an impression as to the time in which regression can be expected to take place; our impression is that when response is satisfactory, it is also early. In such cases, it is noted that regression begins in 2 to 4 weeks after completion of treatment. A minority of cases will diminish perceptibly but incompletely and continue their regression slowly after the second course.

In 1 patient in whom the follow-up course now extends over 5 years, complete regression ensued shortly after a

course of irradiation. Three years later the appearance of enlarging nodes with abscess formation in the treated area brought the patient to another radiologist who was able to produce a prompt regression again. Two years following the second course the patient remains asymptomatic. This patient is an exceptional case and far from typical. Even though our follow-up in many cases extends over a 4 or 5 year period we have found that when exacerbation occurs it usually takes place early. Late exacerbation is so unusual that it raises the question as to whether it really is exacerbation or involvement of adjacent untreated areas. The latter situation can be expected to occur in a few cases where the extent of the disease is not apparent or misjudged at the time of treatment. This source of error will be minimized if careful examination is carried out in order to locate the fields of treatment correctly.

A review of the recent literature reveals a favorable comparison of the results secured by our plan of treatment with the best results secured elsewhere. Generally, plans of treatment elsewhere are extended over a period of a month to a year with total dosage per field as low as 450 r and as high as 1500 r per field, individual treatments of the series being given at intervals of a week to a month. The reason usually stated for such protraction of the treatment is that the chronicity of the disease and the experience of other observers requires such an approach as the best and safest treatment. For example, Hauser<sup>2</sup> secured satisfactory (50 to 100% regression during treatment or within a few months following) results in 88% of his series of cases with tuberculous cervical adenitis by treating at intervals of 10 days for a period of 100 days. These results are among the best reported and agree closely with our own. However, we accomplish this result by treatment on 4

or 5 successive days, in exceptional cases giving a second course 2 months later. This represents an important advantage to the patient in time and convenience and he is more likely to complete the course of treatment than if it is extended over months. Treatment may be given on an out-patient basis, in which case time lost from work or studies is at a minimum. In our series, only 7 of the 31 cases (22%) classified as showing complete regression required a second course of treatment over a specified area. By definition, the patients with incomplete regression or unsatisfactory response have all had more than one course of roentgen therapy.

The availability of streptomycin has led to its increasing use in treatment of various forms of tuberculous involvement, including tuberculous adenopathy. Our experience with streptomycin-treated tuberculous adenitis is limited, as in this institution nearly all such cases are treated by irradiation. To meet the third purpose of this study, therefore, we have relied chiefly on the recent reports<sup>1,4</sup> of the Council on Pharmacy and Chemistry of the American Medical Association. The Sub-Committee on Streptomycin assembled the observations on the use of this drug from widely scattered medical centers and their conclusions probably reflect the most authoritative and recent thinking on the use of specific therapy in tuberculosis and its complications. They found that the effects of streptomycin therapy on tuberculous sinuses have been sufficiently uniform to establish its usefulness. The underlying lesions in these cases were in bone, cartilage or lymph nodes. "A number of these patients have also had one or more groups of firm, non-caseating lymph nodes. The effect of streptomycin on these nodes has been variable. In some instances a definite and prompt reduction in size occurred, while in

others there has been little or no change. There is no obvious reason for the disparity in these results."

In view of the toxicity of streptomycin, careful laboratory supervision and hospitalization are recommended during the course of treatment, which extends from 90 to 120 days. Anything less than a complete course is unjustified. The advantage of radiation therapy is obvious even if from this point of view alone. Results of treatment with radiation lend additional support to our belief that streptomycin therapy might best be reserved for the 15 to 20% of cases which are resistant to adequate treatment by roentgen therapy.

The indiscriminate use of streptomycin introduces the real danger of creating streptomycin-resistant tubercle bacilli. Such a risk is, of course, to be accepted in those forms of tuberculosis which carry a serious prognosis and for which no other adequate means of therapy exist. In cases of tuberculous adenopathy, where so often the disease is of limited extent and the results of irradiation may be so good, the possibility of producing streptomycin-resistant organisms should be avoided.

The report of the Sub-Committee on Streptomycin contains this carefully worded statement which is made without reference to radiation therapy but which must be interpreted as being especially significant in view of the excellent results secured by the radiologist in the treatment of cervical tuberculous lymphadenitis. "For the present, streptomycin should not be used in the treatment of minimal pulmonary tuberculosis or *other lesions that may be expected to clear on older and accepted forms of therapy.*"

Summary. Thirty-seven cases of cervical tuberculous adenitis treated by roentgen therapy and conservative surgical procedures and having adequate treatment and follow-up have been reviewed.

Complete regression of the diseased nodes and healing of sinuses occurred in 84% of the cases; in about 20% of these, a second course of irradiation was necessary to achieve this result. If the patient did not respond properly to the second course of roentgen therapy, no more irradiation was given. This latter group of cases, showing incomplete regression or an unsatisfactory result, comprises 16% of our series.

These results were secured by a plan of treatment extending over a period of 4 to 5 days in contrast with plans of treatment used in other clinics which

call for protraction over a period of several weeks, months, or even a year. The advantages in time and convenience of our plan of treatment are obvious and results are comparable to the best reported in the literature.

For the present, at least, radiation therapy must be regarded as superior to streptomycin in the management of cervical tuberculous adenopathy. Streptomycin might best be reserved for use in the 15 to 20% of all cases where irradiation does not cause complete regression.

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# THE TRANSFUSION OF ARTERIAL HYPERTENSIVE AND NORMOTENSIVE BLOOD INTO HYPERTENSIVE SUBJECTS

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MANY attempts have been made in the past to demonstrate the presence of circulating vasoconstrictor or pressor substances in the blood of hypertensive individuals. As early as 1911 Bröking and Trendelenburg<sup>1</sup>, using frogs, found no greater vasoconstrictor activity in blood from hypertensive patients than in that from normal subjects. Likewise in that year, Stewart<sup>12</sup> did not find pressor effects in dogs injected with small amounts of serum from hypertensive patients. More recent investigations, consisting of direct transfusions of hypertensive blood from man to man by Höst,<sup>6</sup> failed to show pressor activity. Pickering<sup>7</sup> and Prinzmetal, Friedman, and Rosenthal<sup>8</sup> did not find any elevation in blood pressure when they transfused blood from patients with malignant hypertension into patients with a normal circulatory system, even when as much as 2000 cc. of blood was given.

The progressive changes in renal function and renal hemodynamics, associated with hypertensive disease in man are heralded in early stages by a reduction in effective renal blood flow. The rate of glomerular filtration, how-

ever, is usually within the normal range in this state. The ratio between glomerular filtration and the total renal blood flow is increased. In most cases of well established hypertension, there is present a diminution in the renal blood plasma flow and an increase in the filtration fraction. Other changes occur; the maximal tubular excretory capacity and the maximal tubular reabsorption may be reduced. Again, usually in the later stages of the disease, the glomerular filtration rate is reduced.<sup>5</sup>

The experiments here reported were made in an effort to demonstrate pressor or vasoconstrictor substances in the blood of patients with hypertension by using the kidneys of hypertensive individuals as test objects. It was thought that transfusion of blood containing pressor substances by bringing about efferent arteriolar constriction might produce in such individuals a transitory fall in renal blood flow and elevation of the filtration fraction over the pre-transfusion values, whereas such changes might not occur following transfusion of normotensive blood.

Arterial rather than venous blood

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was used because of the possibility that destruction or inactivation of vasoconstrictor or pressor substances might occur during their passage through various arteriolar beds. In some experiments recipients with markedly impaired renal function were studied because of the possibility that the tissues of such patients might inactivate pressor substances more slowly than those of normal subjects.

**Methods.** Six hypertensive patients were each made the recipients of a transfusion of arterial blood from a normotensive donor and from a donor with hypertension. In 1 patient, H. C., normotensive venous blood was also transfused. Of the 6 hypertensive recipients the renal status of 1 was excellent, that of 1 was good, while those of 4 were poor, as evidenced by the clearance of mannitol and para-amino hippurate as well as other renal function studies. In the latter 4 cases there was nitrogen retention.

Suitable donors were typed, their Rh status determined, and their blood cross-matched with that of the recipient within 24 hours preceding the transfusion. Recipients and donors were in the fasting state at the time of the procedure. The glomerular filtration rate and the renal plasma flow were determined by measuring the plasma mannitol and para-amino hippurate (PAH) clearances, respectively. The clearance periods were usually of 20 minutes duration, but were sometimes longer during those periods when blood was being transfused.

In the first experiment, 75 cc. of 2% citrate solution was added to the infusion solution during the 2 pre-transfusion periods as a control; this practice was abandoned in later experiments. Toward the end of the second clearance period, arterial blood was collected from the brachial artery of the donor over the course of 15 to 30 minutes into a flask containing 75 cc. of citrate solution to prevent clotting. This arterial blood was substituted for a very slow intravenous infusion of 0.9 gm. % NaCl which was introduced during the first 2 periods. The other intravenous infusion, containing mannitol and sodium para-amino hippurate in approximately 0.7% solution of NaCl, was maintained at the same rate (4 cc. per minute) as in the preceding periods. Clearance measurements were then continued during 2 periods while the blood was transfused. Two hundred to 450 cc. of blood was introduced in 30 to 60 minutes. Subsequently, observations were made during

2 additional periods (Numbers 5 and 6). In some experiments the blood was replaced by 0.9% NaCl during periods of 5 and 6, the rate of flow being 4 cc. per minute; in other experiments this infusion was discontinued after period 4. An indwelling urethral catheter was used to facilitate collection of urine. Twenty cc. of distilled water and 20 to 50 cc. of air were introduced to insure complete evacuation of the bladder. Blood pressure readings were taken throughout the procedure by the auscultatory method except during one experiment when no observations were made. One group of experiments was done to follow specifically the effect upon blood pressure when blood was transfused into a hypertensive individual with renal insufficiency. Measurements of renal clearance were omitted in this experiment. No elevation in temperature occurred after any transfusion, nor were there other signs of unfavorable reactions.

The experiments were carried out under as similar conditions as possible in order to minimize physical or psychological influences. The same environment was used for all patients. The procedure was explained to the patient as an evaluation of the function of his kidneys. In a given recipient, exactly the same details of experimental procedures were followed using blood from a hypertensive donor as when using the control blood. The measurement of para-amino hippurate in blood and urine was conducted by the method of H. W. Smith and his associates.<sup>10</sup> The measurement of the mannitol was carried out by the method of W. W. Smith *et al.*,<sup>11</sup> as modified by Goldring and Chasis.<sup>5</sup> The determined values of the clearances were corrected to the standard surface area of 1.73 sq. meters, on the basis of height and weight.<sup>2</sup> Techniques employed for calculating the "mannitol blank" varied during the course of this investigation.<sup>4</sup>

**Results.** There was a definite although slight trend upward in the diastolic pressure of all 5 patients after transfusions of hypertensive as compared to normotensive blood (Table 1). There was no consistency, however, in the changes in the clearances of mannitol or para-amino hippurate, or in the filtration fraction when arterial hypertensive or normotensive blood was transfused into 5 hypertensive patients. In some cases alterations in renal hemodynamics which were not duplicated after the transfusion of nor-

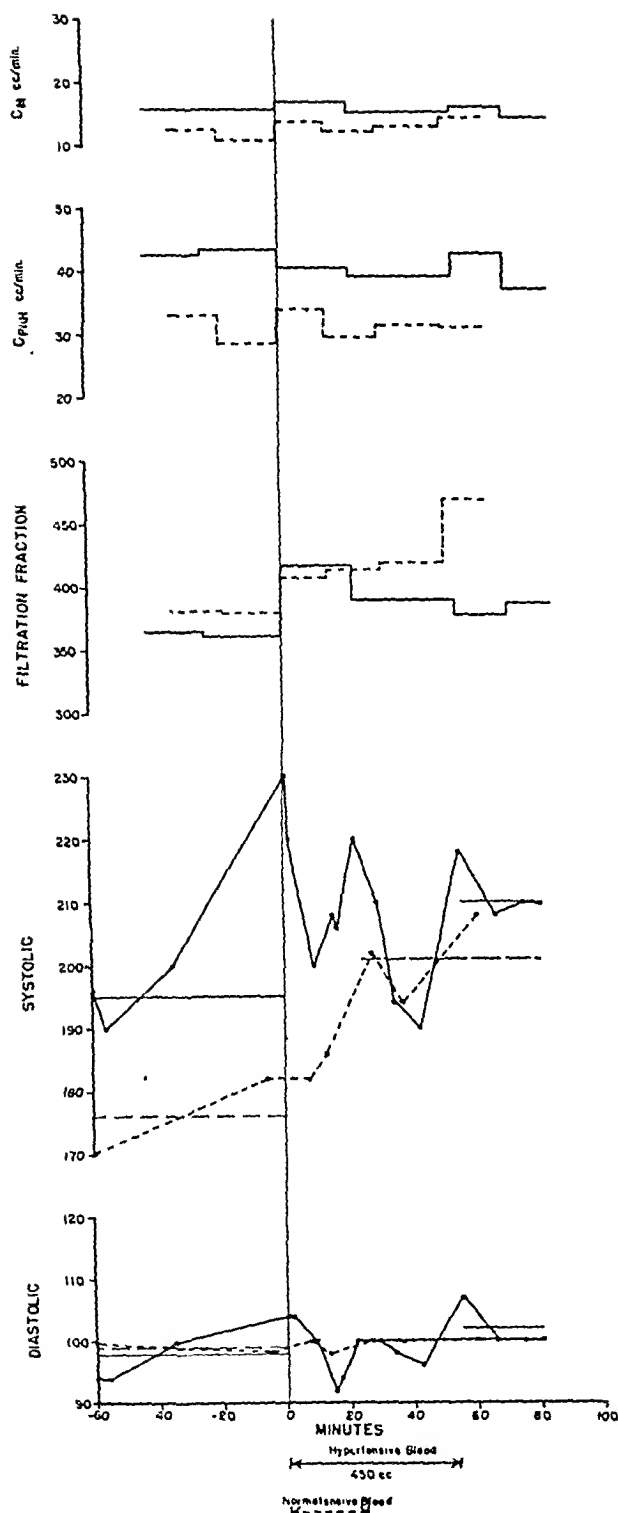


Fig. 1

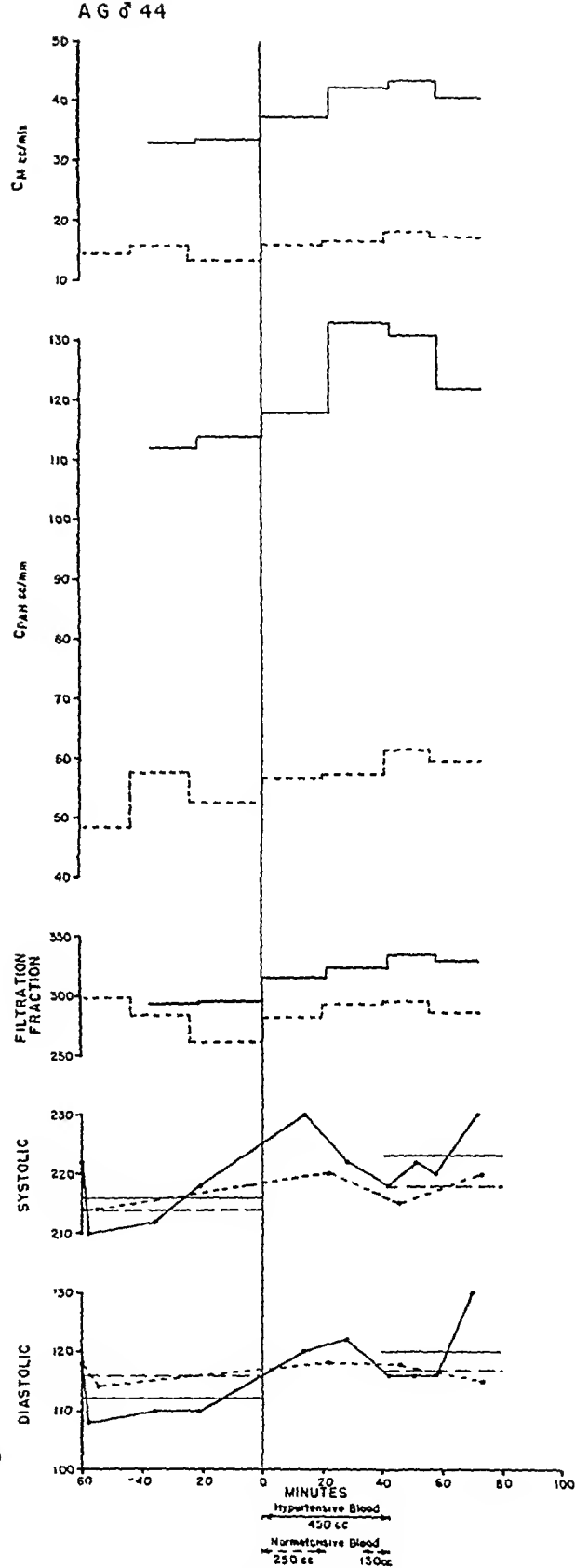


Fig. 2

FIG. 1.—Subject P. R. A comparison between changes in blood pressure, plasma clearance of mannitol, para-amino hippurate, and the filtration fraction after the transfusion of hypertensive and normotensive blood in patients with chronic glomerulonephritis in the uremic stage.

The vertical line at 0 minutes represents the beginning of the transfusions and the horizontal arrows represent their durations.  $C_M$  and  $C_{PAH}$  are the clearances of mannitol and para-amino hippurate respectively. Systolic and diastolic show blood pressure in mm. Hg. The horizontal lines represent averages for the periods indicated. In all figures the solid lines represent values obtained when hypertensive blood was used and the broken lines when normotensive was used.

FIG. 2.—Subject A. G.

TABLE I.

# TRANSFUSION OF ARTERIAL HYPERTENSIVE AND NORMOTENSIVE BLOOD INTO HYPERTENSIVE SUBJECTS

Recipient					Donor					Average Blood Pressure			Max. Change in Plasma Clearance Per Cent of Control Value†					Difference (Hypertensive minus Normotensive)											
Initials	Age	Sex	Blood Group	Rh.	Diagnosis	Renal Function	Initials	Age	Sex	Blood Group	Rh.	Diagnosis	mm. Hg.	mm. Hg.	mm. Hg.	Date of Experiment	Am't. Blood Transfused	Before	After	Change	Max. Change in Bl. Pr.	Period	Manitol	PAH	Filtration	Diastolic Bl. Pr.	Manitol %	PAH %	Filt. Frac. %
P.R.	52	M	A	Pos.	Chronic Glomerulo-nephritis	Poor	A.K.	43	M	A	Neg.	Hypertension	230/120	4/21/47	450	195/98	201/102	+15/+4	+23/+10	6	-8	-13	+8	+9	-35	-15	-15		
A.G.	44	M	O	Pos.	Chronic Pyelo-nephritis	Poor	L.F.	41	F	A	Pos.	Normal	130/80	5/19/47	450	176/99	201/100	+25/+1	+32/+1	6	+27	+2	+23						
							L.M.	38	M	O	Pos.	Hypertension	200/135	6/13/47	450	211/112	223/120	+12/+8	+19/+18	4	+30	+18	+10	+16	+15	+9	+5		
B.B.	23	M	O	Neg.	Chronic Glomerulo-nephritis	Poor	N.P.	36	M	O	Pos.	Normal	118/80	6/27/47	250	214/116	218/117	+4/+1	+6/+2	4	+15	+9	+5						
							L.S.	42	F	O	Neg.	Hypertension	220/98††	4/5/48	350	177/111	197/123	+20/+18	+27/+25	4	+18	+16	+2	+13	+9	+8	+1		
H.C.	40	M	A	Pos.	Chronic Glomerulo-nephritis	Poor	H.L.	24	M	O	Neg.	Normal	110/70	4/12/48	350	178/112	184/119	+6/+7	+12/+12	4	+9	+8	+1						
							L.M.	39	F	A	Pos.	Hypertension**	212/118	10/14/47	350	210/117	206/119	-4/+2	+2/+3	..	..	..	..	..	..	..	..	..	
							G.M.	49	M	A	Neg.	Hypertension	182/106	10/21/47	500	183/119	196/122	+13/+3	+23/+11	..	..	..	..	+13	..	..	..	..	
							*	..	..	A	Pos.	Normal	.....	10/8/47	500*	199/128	198/125	-1/-3	0/-2	..	..	..	..	..	..	..	..	..	
A.F.	39	M	O	Pos.	Hypertension	Excellent	L.S.	42	F	O	Neg.	Hypertension	205/105	8/22/47	400	158/94	162/104	+4/+10	+17/+11	4	†	-6	†	+7	<+14	+26	<-25		
							N.O.	36	M	O	Pos.	Normal	120/70	9/5/47	300	156/96	160/99	+4/+3	+10/+4	4	+1	-32	+31						
C.O.	37	F	A	Pos.	Hypertension	Good	A.K.	43	M	A	Neg.	Hypertension	268/140	4/7/47	200	163/110	.....	.....	.....	4	†	-8	†	..	-12	..	..	..	
							E.B.	23	M	A	Pos.	Normal	130/70	4/1/47	200	.....	.....	.....	.....	4	†	+4	†						

†See text under "Results" for method of computing these values.

††Large blood pressure cuff used, 19 cm. in width.

\*Venous blood from Blood Bank. Normotensive arterial blood could not be obtained at time of experiment.

\*\*"Neutrogenic" classification (9).

†No pronounced elevation in these values; analytical difficulties preclude presentation of absolute values for manitol.

&lt;Signifies "less than."

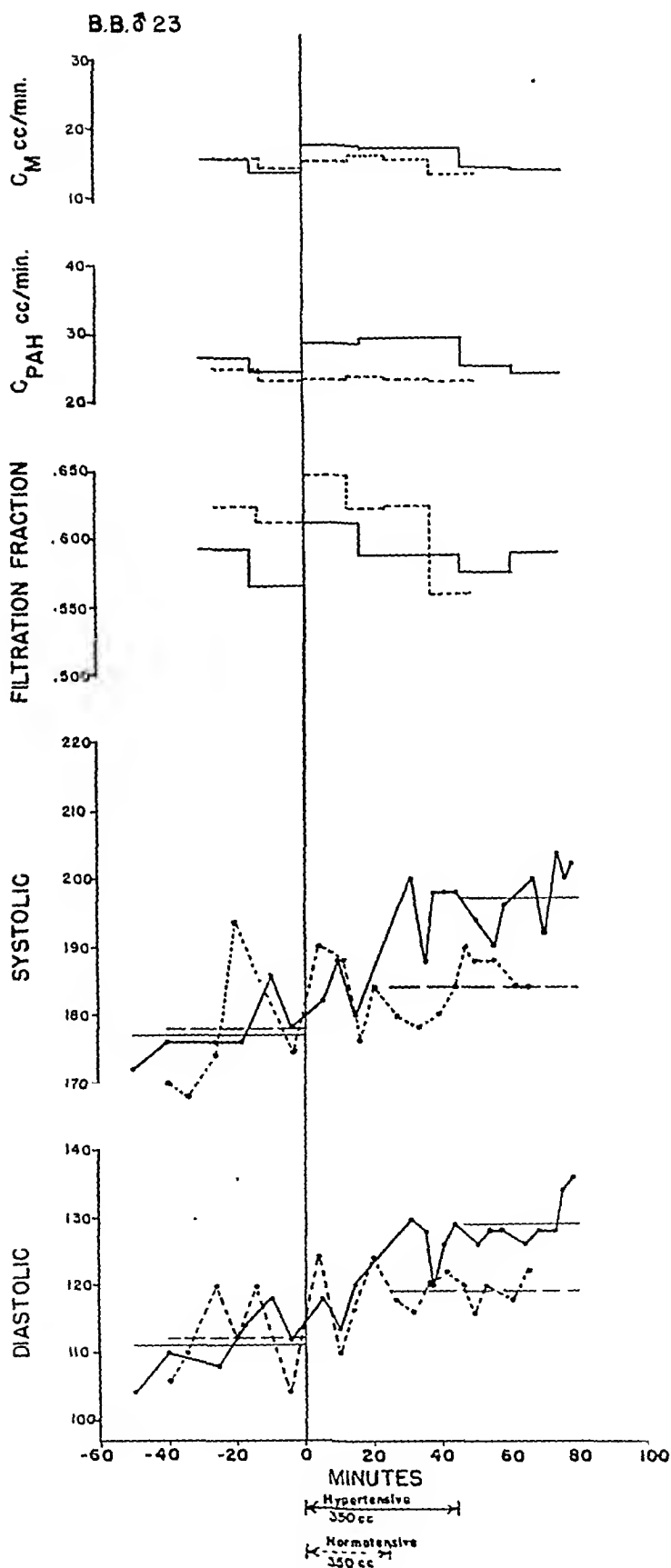


FIG. 3.—Subject B. B. Notations same as Figure 1.



motensive blood did occur (Figs 1-3).

Because of the difficulty of interpretation of small changes in very low clearance values, and the probable interrelationship of blood pressure and renal blood flow under these conditions, the data were evaluated by pairs of experiments, comparing the effects of one kind of blood with those produced by the other. In an attempt to ensure that even slight trends would be recognized, the averages of the PAH and mannitol clearances and of the filtration fraction observed during the 2 control periods in each experiment were calculated. Selection was then made of post-transfusion period in which the PAH clearance diverged most markedly from the control average. The extent of the divergence of the clearances and the filtration fraction in this selected period from the appropriate control averages was expressed as percent of the control value (Table I). The percentages thus obtained for the experiments employing normal blood were then subtracted from those obtained in the experiment using hypertensive blood, and the algebraic differences recorded (Table I, last 3 columns).

The data thus expressed in the last 3 columns of Table I permit an analysis of relative changes in PAH clearance in 5 experiments and in mannitol clearance and filtration fraction in 4. Only differences of 15% or more will be given consideration. Relative to the changes produced by normotensive blood, hypertensive blood lowered all 3 values in 1 subject (P. R.). It elevated the mannitol value in another (A. G.). In a third (A. F.) hypertensive blood elevated the PAH clearance and depressed the filtration fraction. The period of greatest change was usually the second period after administration of blood was started.

Discussion. In order to demonstrate the presence of pressor substances in

the blood of patients with arterial hypertension, at least three avenues of approach might be used to give direct or indirect evidence that such a substance or substances exist. The first might be an increase in blood pressure levels. The second might be reflected in the effect upon renal hemodynamics. The third might be a correlation between renal hemodynamics and blood pressure.

The functional states of the kidneys used in these experiments varied. At first a mild hypertensive was used, C. O., with good renal function, whose blood pressure upon bed rest came down to normal levels. Kidneys in such patients might be sensitive to injected vasoconstrictor substances. No effect upon PAH clearance was noted when hypertensive blood was administered to this patient. In addition, a patient, with sustained, although mild, hypertension, A. F., was studied; his kidneys were apparently normal, as evidenced by a value of 700 cc. per minute for his renal plasma flow and about 115 for his glomerular filtration rate, and a filtration fraction in the neighborhood of .20. Comparison of the effects of transfusion of arterial hypertensive and normotensive blood into this individual revealed relatively less influence of hypertensive blood in elevating the filtration fraction. His diastolic pressure increased slightly after hypertensive blood.

To take the other extreme, kidneys of patients which were poorly functioning might reveal significant changes in the clearance of mannitol and para-amino hippurate, since slight changes in already narrowed arterial beds might be magnified if they occurred. Interpretation of clearance values and decision as to what constitutes a significant change are difficult when severe renal impairment is present. The advanced stages of glomerulonephritis constitute a condition wherein the me-

chanism for the tubular transfer of diodrast is severely damaged, or the loss of renal tubular elements is so great, that the diodrast clearance at low plasma concentrations departs widely from the actual renal plasma flow (3). When experiments on subjects with diminished renal function were done, P. R., A. G., and B. B., the results were not consistent, although changes in the clearances of mannitol, PAH, or in the filtration fractions occurred in 2, P. R. and A. G. The diastolic pressure, however, rose in those two in which these changes were least, A. G. and B. B.

On the basis of these inconsistent results and the variable state of the kidneys of the recipients, it is impossible to ascribe the changes found to the presence in hypertensive blood of substances affecting renal arterioles as measured by clearance methods. On the other hand, the fact that hypertensive blood tended to elevate the blood pressure of the recipients to a greater degree than did normotensive blood is suggestive of the presence of pressor substances. Since the transfusion of hypertensive blood preceded

that of normal blood in all instances, except the experiment on H. C., it is possible that the greater pressor effect of the former may have been actually due to the subject's greater apprehension during the initial experiment. The relation between blood pressure changes and those occurring in the kidney could not be correlated in these experiments.

**Summary.** 1. Six hypertensive patients were transfused with arterial hypertensive and later with normotensive blood. The renal plasma flow and glomerular filtration rate were measured in 5, and the blood pressure in 5, before, during and after transfusion.

2. No consistent changes were noted in glomerular filtration, renal plasma flow, or filtration fraction following the transfusions, although in some cases differences did occur.

3. Hypertensive blood tended to elevate the diastolic blood pressure of the recipients to a greater extent than did normotensive blood.

4. These experiments suggest, but do not prove, the presence of pressor substances in the arterial blood of hypertensive individuals.

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# THE INFLUENCE OF ALCOHOL ON THE INTRAVENOUS GALACTOSE TOLERANCE TEST

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REPORTS concerning the acute effects of ethyl alcohol upon hepatic function have been conflicting.<sup>5,21,28,35,43</sup> However, a number of investigators have indicated that the ability of healthy adults to utilize galactose is impaired by the ingestion of ethyl alcohol.<sup>4,12,34,40,42</sup> The concentration of galactose in the blood, when measured, was found to be abnormally high and the duration of galactosemia abnormally prolonged when the test dose of the sugar was immediately preceded by alcohol. Galactosuria was increased as well. However, the published observations neither establish the minimal effective dose of alcohol nor the duration or site of its action. In only one study<sup>10</sup> was the possibility of altered intestinal absorption of the sugar excluded by its intravenous administration, but the injection was prolonged over a 30 minute period. Therefore, it seemed desirable to define further the influence of alcohol on galactose tolerance.

**Materials, Experimental Procedure, and Methods.** A total of 46 intravenous galactose

tolerance tests were performed on 19 individuals including 15 healthy adults, 2 patients with cirrhosis, 1 with hyperthyroidism, and 1 with psychoneurosis. The subjects were allowed water, but not food, during an overnight fast and were kept at bed rest or restricted activity. Each one voided immediately beforehand, and then had his urine collected during the experimental period. Galactose was administered intravenously, as a 50% solution in distilled water. Dosages of 0.4, 0.5, and 0.6 gm. per kg. of body weight were employed and the injections were completed within 3 to 7 minutes. Venous blood was obtained immediately before the injection and at 15, 45, and 75 minutes after its mid-point. Samples (2.0 ml.) of the oxalated whole blood were fermented to remove glucose by continuous shaking with 6 cc. of 20% bakers' yeast for 30 minutes at room temperature. Deproteinization was then accomplished by the addition of zinc sulfate and sodium hydroxide.<sup>38</sup> Aliquots (5.0 ml.) of the blood filtrates (corresponding to 0.4 ml. of whole blood) were analyzed in duplicate for galactose by the iodimetric method of Somogyi, as were the urine samples.<sup>39</sup> Recoveries of known amounts of galactose added to oxalated whole blood were complete and were not altered by addition of ethyl alcohol to the blood *in vitro* or when the blood donor had ingested alcohol.<sup>40</sup> Moreover, alcohol did not increase the concentration of non-glucose reducing substances in the blood blanks.

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\*\* Non-fermentable reducing substance was detectable in the fasting blood samples in only 8 of the 46 tests at concentrations of 4 to 19 mg. per 100 cc. In these 8 tests galactose concentrations were calculated at the difference between total non-glucose reducing substance and the observed "blood blank."

The response of 10 of the subjects to a standard dose of galactose administered intravenously was first established in one or more studies. Subsequently, the effect of ethyl alcohol ingestion on the blood galactose levels and on the excretion of this sugar in urine during an otherwise identical test was determined. A single dose of 95% ethyl alcohol in amounts of 0.03 to 0.40 cc. per kg. of body weight was given in 100 cc. of water at an interval which varied from 15 minutes to 24 hours before the administration of the sugar. To test the specificity of the influence of alcohol on galactose tolerance, levulose tolerance tests<sup>7,8,38,39</sup> and glucose tolerance tests<sup>7,27,38,39</sup> were performed in 8 experiments with, and 6 without, preliminary administration of ethyl alcohol in doses of 0.30 cc. per kg. In 6 subjects, the rate of removal of bromsulfalein from the serum was measured with and without previous ingestion of alcohol.<sup>36</sup>

**Results. Galactose Tolerance** (Table 1). The control galactose tests of the healthy subjects are in approximate agreement with previously reported normal values.<sup>1,2,3,13,18,22,24,37</sup> One subject (B.J.K.) received 0.4 gm. of galactose per kg. of body weight on one occasion and 0.6 gm. per kg. at another time. The blood levels at each point in the curve were distinctly lower following the smaller dose. The levels

observed in the group of 5 subjects receiving 0.5 gm. per kg. were not apparently different at any time interval from those found in the group of 5 given 0.6 gm. per kg. The patient with hyperthyroidism had a normal galactose tolerance test (Table 1), whereas the 2 subjects with cirrhosis of the liver had impaired tolerances (Table 3). The small magnitude of variations in repeated tolerance tests carried out under standard conditions in the same subject is evident from the results of the 2 studies performed 6 weeks apart on J.R. and the 5 on J.T. during one month (Tables 1 and 2).

*Effect of alcohol on the galactose tolerance* (Table 2). The galactose tolerance test was significantly altered in all 10 subjects without liver disease when 0.26 to 0.40 cc. of ethyl alcohol per kg. of body weight was ingested 15 minutes before the injection of the sugar. The decreased rate of removal was most evident in increased galactosemia at 45 and 75 minutes, although higher blood levels were sometimes observed at 15 minutes. An increase in

TABLE 1.—INTRAVENOUS GALACTOSE TOLERANCE TESTS IN HEALTHY ADULTS

	Galactose Injected (gm. per kg.)	Age (years)	Sex	Body Weight (kg.)	Blood galactose (mg. per 100 cc.) <sup>o</sup>			Excretion in 75 minutes	
					Time (minutes)			Urine (cc.)	Galactose (gm.)
LG	0.6	27	M	68	125	27†	12	100	4.6
JCR	0.6	33	M	70	150	30	10	103	3.5
JP	0.6	31	M	66	171	76	10	137	5.5
JM	0.6	19	F	57	209	72	12	—	—
BJK(a)	0.6	22	F	60	191	74	18	103	4.3
JR (a)	0.5	34	M	65	157	30	11	195	2.1
JR (b)	0.5	34	M	65	147	25	14	—	—
JT	0.5	31	M	77	147	56	16	114	5.4
FM	0.5	27	M	63	152	50	16	75	4.8
DG	0.5	23	F	52	131	7	3	83	1.9
MC†	0.5	27	F	50	167	57	11	205	2.2
BJK(b)	0.4	22	F	60	86	18	6	78	2.0

<sup>o</sup> Values for blood galactose at 15, 45, and 75 minutes are corrected for blood blanks.

† = 49 minutes.

‡ = Hyperthyroid.

§ The analytical method used in the present study permitted determination of blood galactose in concentrations as low as 5 mg. per 100 cc. Galactose has invariably been found in the blood at 75 minutes in concentration of less than 21 mg. per 100 cc. Investigators who report complete removal of galactose from the blood 75 minutes after its intravenous administration in comparable dosage,<sup>3,13,22</sup> have employed analytical methods which are less sensitive at low levels.

the urinary excretion of galactose was also apparent in most instances, but the degree of galactosuria in control tests had been quite variable. Significant galactosemia persisted for at least 120 minutes in the one subject (L.G.) whose blood level was determined after this time interval. In addition, alcohol in the same dosage produced a delay in galactose removal from the blood on the 4 occasions when it was taken 1.0 to 1.25 hours before the sugar. No alteration of the galactose tolerance curve was noted in the 2 experiments in which the interval

between alcohol and galactose administration was extended to 2 hours, nor was any effect apparent in 7 other studies carried out 3, 6, 12, and 24 hours after alcohol ingestion. Less marked but still definitive alteration of the tolerance test was observed when 0.16 to 0.20 cc. of alcohol per kg. was ingested 15 minutes before the test in 3 experiments. Doses of 0.13 cc. per kg. or less in 4 tests had no demonstrable effect on the blood levels.

The results recorded in Table 3 indicate that alcohol produced no definitive evidence of further impair-

TABLE 2.—INTRAVENOUS GALACTOSE TOLERANCE TESTS FOLLOWING THE INGESTION OF ALCOHOL

	Age	Sex	Body Weight (kg.)	Interval between alcohol & galactose (hours)	Dosage of alcohol (cc./kg.)	Blood galactose (mg. per 100 cc.)			Excretion in 75 minutes	
						Time (minutes)			Urine (cc.)	Galactose (gm.)
						15	45	75		
JCR	33	M	70	0.25	0.03	176	54	23	178	16.2
JT	31	M	77	0.25	0.06	123	35	9	96	5.7
FM	27	M	63	0.25	0.10	—	—	10	96	4.2
JT	31	M	77	0.25	0.13	157	—	17	224	12.3
CM	15	M	61	0.25	0.16	141	75	31	212	14.7
LF	35	F	50	0.25	0.20	162	94	37	125	8.7
AS	64	M	54	0.25	0.20	—	—	32	121	2.9
JT	31	M	77	0.25	0.26	179	106	74	264	8.8
JM*	19	F	57	0.25	0.26	184	134	85	157	2.2
LG*	27	M	68	0.25	0.29	152	94	65**	363	7.6
JCR*	33	M	70	0.25	0.29	195	111	59	180	8.7
JR	34	M	65	0.25	0.30	168	103	67	620	12.0
RO	23	F	60	0.25	0.33	—	—	75	190	6.2
BJK	22	F	60	0.25	0.33	182	121	82	125	2.2
AB‡	15	F	55	0.25	0.36	161	—	60	68	3.9
IL	24	F	54	0.25	0.37	156	—	68	162	2.7
MC†	27	F	50	0.25	0.40	163	—	54	430	4.1
JT	31	M	77	1.00	0.30	—	—	77	230	6.6
FM	27	M	63	1.00	0.30	—	—	68	256	7.4
RO	23	F	60	1.17	0.33	172	—	26	139	6.3
JT	31	M	77	1.25	0.26	—	—	39	114	5.3
LT	59	F	44	2.00	0.30	—	—	8	146	1.8
AS	64	M	54	2.00	0.30	—	—	20	143	2.3
RO	23	F	60	3.00	0.33	196	—	15	90	7.0
JT	31	M	77	6.00	0.26	180	76	18	96	5.6
JT	31	M	77	12.00	0.26	175	52	11	77	3.9
RO	23	F	60	12.00	0.33	175	79	20	124	4.2
JT	31	M	77	24.00	0.26	155	53	15	122	5.6
IL	24	F	54	24.00	0.37	150	—	19	81	2.2
LF	35	F	50	24.00	0.40	120‡	—	12‡	123	0.5

\* These 3 subjects received 0.6 gm. galactose per kg. of body weight. All others were given 0.5 gm. per kg.

\*\* Decreased to 39 mg. per 100 cc. at 120 minutes.

‡ Psychoneurosis.

† Hyperthyroidism.

‡ Blood taken at 20 and at 80 minutes respectively.

ment of galactose tolerance in the 2 patients with cirrhosis of the liver.

The administration of alcohol had no discernible effect on the utilization of glucose or levulose nor did it change the fasting blood sugar (Table 4). Neither did the alcohol alter the bromsulfalein excretion rate in the 6 subjects tested. Thirty minutes after the intravenous administration of 5 mg. per kg. of body weight, less than 10 mg. per 100 cc. of the dye was detectable in the serum of the healthy subjects. Similarly the 2 patients with cirrhosis of the liver exhibited no further impairment of their already diminished capacity to excrete the substance. These data have not been tabulated.

**Discussion.** The results demonstrate

clearly that small amounts of ethyl alcohol produce significant and consistent abnormalities of the galactose tolerance test in healthy adults. Blood levels of galactose at 75 minutes increased in some instances as much as 5-fold following alcohol ingestion, and distinct elevations were also observed at 45 minutes. The 15 minute values showed less consistent changes, presumably because these were in part determined by the speed of injection and the rate of diffusion through the body fluids. Slight delay in galactose removal was observed when alcohol was taken in quantities as small as 0.16 cc. per kg. of body weight. Stentsam<sup>40</sup> has reported increased galactosemia in one healthy subject who received as little as .03 or .08 cc.

TABLE 3.—INTRAVENOUS GALACTOSE TOLERANCE TESTS WITH AND WITHOUT PRELIMINARY ALCOHOL INGESTION IN SUBJECTS WITH CIRRHOSIS OF THE LIVER.

	Age	Sex	Body Weight (kg.)	Dosage of alcohol* (cc./kg.)	Blood galactose (mg. per 100 cc.) Time (minutes)			Excretion in 75 minutes	
					15	45	75	Urine (cc.)	Galactose (gm.)
JC (a)	50	M	66	0	144	84	42	154	1.8
LB (a)	48	M	78	0	159	—	88	210	3.6
JC (b)	50	M	66	0.3	165	—	44	210	2.7
LB (b)	48	M	78	0.3	157	—	82	83	2.5

\* Given 15 minutes before galactose.

TABLE 4.—GLUCOSE AND LEVULOSE TOLERANCE TESTS WITH AND WITHOUT PRELIMINARY INGESTION OF ALCOHOL.

Subject	Age	Sex	Body Weight (kg.)	Dosage of alcohol° (cc./kg.)	0	Blood sugar (mg. per 100 cc.) Time (minutes)				120
						30	60	90		
A. Glucose 25 gm. intravenously										
JR	34	M	65	0	79	—	—	—	73	
				0.3	84	—	—	—	67	
AA	29	M	60	0	75	—	—	—	72	
				0.3	81	—	—	—	57	
TZ	26	M	70	0	89	—	—	—	91	
				0.3	88	—	—	—	75	
AO	50	F	60	0.3	87	—	135	—	74	
B. Levulose 40 gm. orally										
JR	34	M	65	0	90	126	130	71	77	
				0.3	88	120	126	82	70	
GM	60	M	95	0	80	102	86	77	82	
				0.3	82	102	93	66	69	
AD	24	M	90	0	73	86	86	77	75	
				0.3	73	95	90	65	54	
IL	24	F	54	0.3	86	105	105	78	77	

\* Given 15 minutes before administration of sugar.

of alcohol per kg., but only small doses of galactose were given and the sugar was taken by mouth.

In the present study the degree of abnormality of the tolerance test was proportional to the dose of alcohol over the low dosage range studies. Moreover, the abnormality was demonstrable for a relatively short time after alcohol ingestion. This would be anticipated if the effect of alcohol on galactose removal was dependent on the blood alcohol concentration during the test.<sup>11</sup> It seems probable that doses of alcohol larger than 0.4 cc. per kg. of body weight might well alter the galactose tolerance test for longer periods. Indeed, suggestive confirmation of this possibility has been obtained in one subject who displayed an abnormal tolerance test 60 hours after a very large, but unmeasured, intake of alcohol.

It is apparent that the elevated concentrations of galactose in the blood following ethyl alcohol ingestion were the results of retarded removal of the sugar from the blood stream, since it was administered by the intravenous route, and urinary excretion usually accounts for only a small fraction of the galactose leaving the circulation in man. In these experiments, the increased galactosuria noted after alcohol proved that elevation and prolongation of galactosemia could not be related to decreased renal excretion of the sugar. Since the analytical method for galactose actually measured the total concentration of unfermentable reducing substances in the blood filtrate, the possibility that some other non-fermentable reducing compound enters the blood stream while galactose is being removed at a normal rate might be considered. However, the failure of such a substance to appear in the blood when alcohol alone is

given and the normal glucose and levulose tolerance tests after alcohol ingestion eliminate such an hypothesis from serious consideration. It is reasonable to assume that the removal of galactose is delayed because of interference with its uptake and conversion to glycogen by the liver. In the hepatectomized dog, galactose cannot be utilized as a source of blood glucose and the rate of galactose removal from the blood is extremely slow if renal excretion is prevented.<sup>9</sup> All the available evidence derived from animal experimentation points to the dominant role of the liver in galactose utilization.<sup>16,17</sup> Clinical observations indicate that only in hepatic disease is the intravenous galactose tolerance test significantly altered.<sup>1,2,3,13,18,22,24,37</sup> No differences have been detected between the persistently abnormal galactose tolerance test of patients with liver disease and the transiently impaired curves of normal subjects given alcohol. The failure of alcohol further to impair the galactose tolerance in patients with hepatic disease<sup>4,34,40</sup> lends additional support to the view that the liver is the site of the alcohol action.

Although the argument is strong that alcohol influences galactose removal by impairing hepatic uptake, and presumably the conversion of galactose to glycogen, there is little support for the view that any general impairment of liver function is produced by the doses employed. Indeed, the failure of alcohol to decrease levulose tolerance suggests a highly specific action of alcohol on the hepatic enzyme systems involved in handling galactose.<sup>6</sup> Moreover, no impairment of bromsulfalein excretion was demonstrated in the present study. MacNider<sup>28</sup> observed temporary impairment of phenoltetrachlorophthalein excretion in dogs poisoned with large

\* Recently, the identification of an enzyme, "galactokinase", which catalyzes the conversion of galactose to galactose-1-phosphate by the yeast *Saccharomyces fragilis* has been reported.<sup>41</sup> It is of interest that one of the characteristic properties of this enzyme is that its activity is easily impaired by treatment with alcohol.

doses of ethyl alcohol, 10 to 15 cc. of a 40% solution per kg., repeated as required to maintain a state of seminar-cosis for 12 to 24 hours. Rosenthal<sup>35</sup> gave dogs smaller doses of ethyl alcohol (2 cc. of a 98% solution per kg.) and found normal concentrations of urine urobilinogen and serum bilirubin with only a slight delay in bromsulfalein excretion 2 to 6 hours later. In proportion to body weight, the dose employed by Rosenthal is almost 7 times as large as the quantity required to produce marked impairment of galactose tolerance in man. Little has been published concerning the immediate effects of alcohol on other tests of liver function in human subjects. The few available reports<sup>5,21,43</sup> deal with observations made after, but not during, an episode of acute alcoholism. The problem deserves further investigation with the aid of modern sensitive methods.<sup>44</sup> However, it seems clear that the ability of the liver to handle galactose is peculiarly susceptible to impairment by alcohol. The observation that alcohol interferes with the removal of galactose from the blood is of practical importance in the interpretation of galactose tolerance tests used in the evaluation of hepatic function or de-

signed to reflect rates of intestinal absorption.<sup>2</sup> It is of even greater theoretical interest with respect to the well recognized clinical association between alcoholism and portal cirrhosis of the liver<sup>14,19,23,31,33</sup> and the possible role of alcohol in the pathogenesis of this disease.<sup>6,14,15,25,26,31</sup> Finally, it has been suggested,<sup>10,29,30,32</sup> on the basis of studies concerning infants with chronic galactosemia, that the continued failure properly to utilize galactose derived from the diet may of itself lead to hepatic damage. Further evidence in support of this hypothesis has been presented elsewhere.<sup>20</sup>

**Summary.** Ethyl alcohol in small doses temporarily reduced the galactose tolerance of healthy adults, but did not influence the already abnormal tolerance tests of 2 patients with cirrhosis of the liver.

Although the abnormal tests following alcohol ingestion were almost certainly due to impairment of the ability of the liver to remove galactose from the blood stream, there was no concomitant impairment of bromsulfalein excretion or of levulose and glucose tolerance.

The significance of these findings is discussed.

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# CERTAIN EFFECTS OF SALT POOR HUMAN ALBUMIN IN CASES OF HEPATIC DISEASE\*

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RECENT studies<sup>1,7,9,12,16</sup> have indicated considerable doubt about the benefit to be expected from human albumin therapy in cases of cirrhosis of the liver. In some instances good results were noted in the treatment of ascites, especially if the patients were tapped dry before administration of the albumin.<sup>1</sup>

We have been interested in following the effects of considerable amounts of salt poor human albumin in cases of liver disease of various types. In previous reports little mention has been made of untoward effects. We have been impressed in particular by an unfavorable water retention in some cases, often associated with fever and pulmonary edema. The purpose of the present communication is to describe our observation in these cases and at the same time make some comment on the value of salt poor human albumin in the treatment of liver disease.

**Material and Methods.** Salt poor human albumin has been administered to a number of patients suffering from various types of hepatic disease, on the Medical Service of the University of Minnesota Hospital. Six of these have been studied in more detail and form the material for the present communication. Two of the 6 were chronic alcoholics and were suffering from so-called alcoholic cirrhosis of the liver; three had cirrhosis believed to be a sequel of sporadic infectious hepatitis, and one had homologous serum hepatitis.

The following studies were carried out:

Serum bilirubin,<sup>3</sup> urine urobilinogen,<sup>15</sup> feces urobilinogen,<sup>15</sup> cephalin cholesterol,<sup>5</sup> thymol turbidity,<sup>10</sup> serum cholesterol and cholesterol esters.<sup>14</sup>

The salt poor human albumin was provided through the courtesy of the American National Red Cross in a 25% solution, the solvent consisting of a 0.3 M sodium chloride solution. The desired amount of albumin, ranging from 25 to 100 gm. per injection, was diluted with 500 to 1000 cc. of 5% dextrose in distilled water and administered intravenously at the rate of about 250 cc. per hour.

Liver biopsy under peritoneoscopic control was performed as previously described.<sup>6</sup>

The "liver diet" which will be referred to consists of 350 gm. of carbohydrate, 150 gm. protein, and 100 gm. of fat per day.

**Protocols.** CASE 1. E. R., a 64 year old white male undertaker, entered the hospital on Oct. 24, 1947. He complained of pruritus, anorexia, nausea, jaundice and light colored stools for the previous 2 weeks. A malignant melanoma had been removed 2 years before. A mesonephric ridge tumor was removed in May, 1947, at which time he had been given 14 blood transfusions. Physical examination revealed icteric sclerae, multiple petechiae, foetor hepaticus, and hepatomegaly to the level of the umbilicus. The spleen was palpable 1 inch below the left costal margin. The liver function studies are shown in Fig. 1. On Oct. 24 he was placed on a liver diet, multivitamins, and high caloric feedings. Increasing jaundice, anorexia and diminution of the size of the liver developed. The patient was somnolent and foetor hepaticus was pronounced. Six hundred gm. of salt poor human albumin were given between Nov. 7 and 12, incl. During this period the patient began to improve and went on to rapid and evidently complete recovery. At first this was attributed

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to the apparent effect of the serum albumin. Though the patient did not appear to improve until the third day of albumin therapy, the attending physician felt convinced of its value; in fact he regarded it as little short of life saving. Nevertheless, it is seen in Fig. 1, that there was a significant decrease in the serum bilirubin just prior to the beginning of albumin therapy, so that the question of coincidental spontaneous recovery is obvious. No untoward effects of the albumin were noted in this case.

CASE 2. O. S., a 42 year old white housewife and tavern operator, was admitted on

riched milk mixture.\* No significant improvement was noted. From Jan. 26, 1948, to Feb. 4, 1948, inclusive, salt poor human albumin was administered daily to a total of 950 gm. The effect on the serum albumin, serum globulin, and other observations are shown in Fig. 2. Of particular interest is the reversal of the albumin-globulin ratio and the marked decline of the thymol turbidity, without change in the cephalin flocculation. No diuresis was observed; in fact, the urine volume diminished somewhat, and the patient gained weight. A liver biopsy at this time revealed a severe fatty cirrhosis with considerable degen-

TABLE 1.—OBSERVATIONS IN CASE 3 (T. C.)

Observation or material given	TABLE 1.—OBSERVATIONS IN CASE 3 (P. C.)														
	Day of Study — May, 1948														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Salt Poor Human Albumin. Grams (Intravenous)						50	100	100	100	100	100				
5% Glucose in Distilled Water (Liters)						0.5	1.0	0.8	0.8	0.6	0.8				
Weight (lbs.)		144	143	142	144	141	143	143	144		149	151		Died	
Urine Volume (L.)	1.9	2.0	2.8	2.2	2.5	1.1	3.0	2.0		2.1	1.0	0.9			
Bilirubin (mg./100cc.)															
One Minute		1.8				2.1			1.6		1.5		2.4		
Total		3.8				4.6			2.3		4.9		7.9		
Cephalin Cholesterol (24 and 48 hr.)		3+4+							3+4+		3+4+		3+4+		
Thymol Turbidity (Units)		7.8				10.8			5.5		5.5		5.5		
Alkaline Phosphatase (Bodansky units)		6.1				5.9			5.3		3.8				
Cholesterol (mg. per 100 cc.)															
Total		146				160			110		130		72		
Esters		57				83			57		95		28		
Serum Proteins Gm./100 cc.															
Albumin						2.7			4.8		5.3		5.3		
Globulin						4.8			3.2		2.9		3.3		

January 13, 1948. She complained of vomiting and jaundice for 6 weeks prior to admission. A history was obtained of poor appetite, low protein intake, and alcohol ingestion for 6 years previous to entry. Spider naevi, ascites, and moderate edema of the lower extremities were noted on physical examination. The liver was enlarged to 10 cm. below the right costal margin in the midclavicular line. For the first 13 days she was treated with a liver diet supplemented with an en-

erative change represented by open spaces.\*\* There was increasing evidence of hepatic insufficiency. Somnolence, intermittent febrile hepatitis, and increasing peripheral edema were observed. From Feb. 5th to Feb. 28th, 1500 cc. of 20% glucose containing 75 units of insulin were administered daily. From Feb. 11 to Feb. 28, 10 cc. of intraheptol were also administered daily. Definite improvement had already begun, however, on Feb. 11th. This was ushered in with a con-

\* Milk 6-S. Miltene 1. The latter is a dehydrated milk-calcium caseinate-lactose powder provided through the courtesy of the Dintene Corporation, Minneapolis, Minn.

\*\* Photomicrographs are reproduced elsewhere.<sup>17</sup>

siderable diuresis, followed by improved appetite, mental clarity and diminishing jaundice. Over a period of 2 months the jaundice entirely disappeared. At the present time the patient feels very well. This case was instructive because of the obvious water retention, and gain in weight in spite of elevation of the serum albumin to 5.0 gm. per 100 cc. This was associated with deterioration of her general status, rapid improvement occurring, however, upon administration of hypertonic glucose solution.

CASE 3. T. C., a 41 year old white road construction laborer, entered the hospital on March 15, 1948. Two years previously, in March, 1946, he had noted dark urine, weakness, and anorexia. In April 1946 an appendectomy was performed. In June 1946,

May 12 he was given a total of 550 gm. of salt poor human albumin. On May 11 he complained of a severe headache and a feeling of tiredness. He appeared quite lethargic. On May 12th, moist râles were noted at the lung bases. Fever up to 102° was noted on May 13th. On the same day a severe nose bleed occurred. He was apprehensive and sweating profusely. Dyspnea was observed the following day and his venous pressure was 17 cm. On May 14th his blood volume was 6.85 liters as compared to a statistical normal of 5.6 liters (Evans blue dye method). The hematocrit was 33.6%, plasma volume 4.46 liters.

Early in the afternoon of the 14th, 600 cc. of blood was removed, following which the patient felt considerably improved. About

TABLE 2.—LIVER FUNCTION STUDIES BEFORE AND AFTER THE ADMINISTRATION OF SALT POOR HUMAN ALBUMIN, IN CASES 4, 5 AND 6

Observation	Case 4, H. A.				Case 5, C. A.			Case 6, D. M.		
	Before 2-9-48	2-16-48	After 2-27-48	3-5-48	Before 4-19-48	After 4-30-48	5-8-48	Before 2-11-48	After 2-18-48	3-1-48
Cephalin										
Cholesterol										
(24 and 48 hr.)	3+4+	3+4+		3+4+	3+4+	3+3+		3+4+	3+4+	3+4+
Thymol Turbidity										
(units)	2.9	1.7		3.6	6.5	3.9		9.2	5.5	7.8
Serum Bilirubin										
One Minute	1.0	1.0		0.6	2.4	2.1	patient	12.5	11.2	9.3
Total (mg./100 cc.)	3.5	3.6		3.5	4.9	4.2	died	23.5	21.5	15.6
Serum Protein										
(Gm./100 cc.)										
Albumin	2.8	3.9	3.2		1.2	2.2		2.7	5.3	4.3
Globulin	3.7	2.1	3.1		5.8	4.3		4.2	2.7	3.1
Cholesterol										
(Mg./100 cc.)										
Total	140	66		98	56	36		106	56	72
Esters	90	33		50	7	9		29	21	14
Alkaline Phos-										
phatase	6.1	2.8		5.0	1.5	1.4		16	5.0	8.1
(Bodansky units)										

jaundice, anorexia, dark urine, and weakness developed. These recurred in February 1947 and again in June 1947. He was first seen in the University Hospital in August 1947. At that time, a liver biopsy revealed portal cirrhosis. He improved somewhat, was discharged on August 15 and felt fairly well until November 1947 when his symptoms recurred, and steadily increased in severity. On admission, the significant physical findings were lethargy, palmar erythema, spider nevi, ascites, splenomegaly, and an enlarged firm liver. From March 23 to May 7 he received the liver diet, enriched milk mixture, and 10 cc. daily of intraheptol. No significant improvement was observed. From May 7 to

midnight, however, he became much more dyspneic, and died rather suddenly at 12:15 A.M. The significant findings at necropsy were as follows: Pulmonary congestion and edema, bilateral pleural effusion, ascites, and a diffuse, non fatty cirrhosis of the liver. The latter was classified as probably post infectious in character. The significant laboratory data in Case 3 are given in Table 1.

Again it is clear that there was marked water retention as a result of the albumin therapy with gain in weight and severe pulmonary edema in spite of an elevation of the serum albumin to 5.3 gm. per 100 cc. In retrospect it seems possible that the fatal outcome might have been avoided if plasma-

phoresis had been done when the magnitude of increase of the plasma volume was learned. Unfortunately there was so much apparent improvement following the removal of 600 cc. of blood, that a sense of false security was gained.

CASE 4. H. A., a 56 year old white liquor salesman entered the hospital on Jan. 31, 1948. He complained of jaundice and intermittent dark urine. For 2 years prior to admission he had noted transient jaundice and ankle edema. A mild psychic disturbance was noted in Oct. 1947. Several paracenteses had been performed a few months

red. A chest film on May 14th revealed congestion of the lungs and a suggestion of infiltration in the lower portion of the left lung. The changes in liver function were not remarkable (Table 2).

CASE 5. C. A., a 68 year old white housewife, entered the hospital on Feb. 22, 1948. For the previous 2 months she had noted weakness, anorexia, nausea, vomiting, jaundice, and pruritus. She stated that her stools had been light and her urine dark. Diabetes mellitus had been diagnosed by her physician one month before admission. There had been a 40 pound weight loss in the last 4 months,

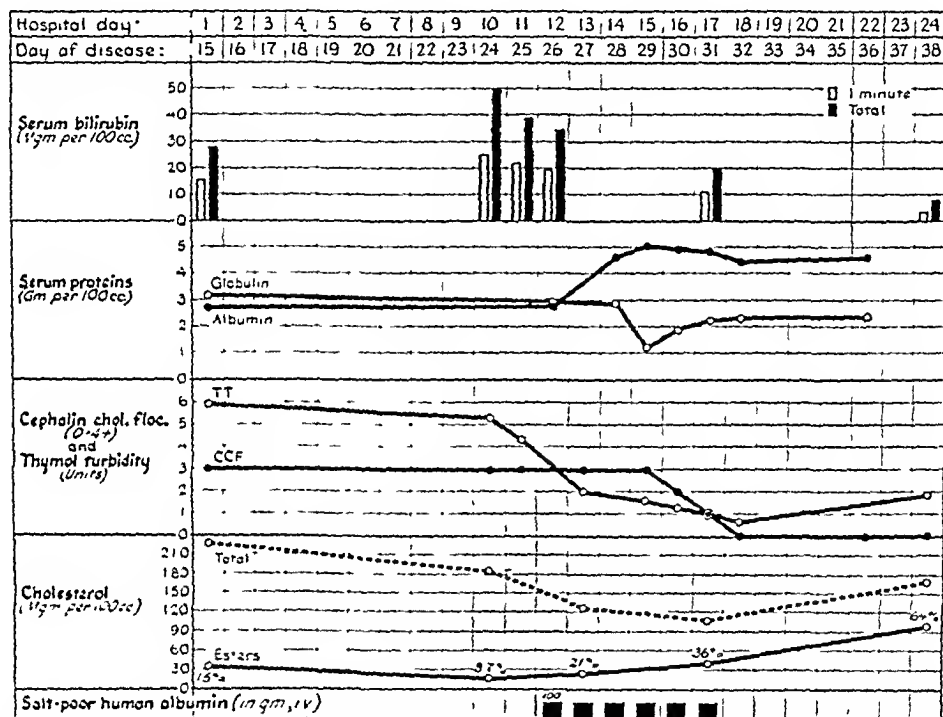


FIG. 1.—Serial liver function studies in Case 1, before and after administration of salt poor human albumin (E. R., male, age 64).

prior to admission. A long history of alcoholism was obtained. Physical examination revealed icteric sclerae, spider nevi, foetor hepaticus, and ascites. The liver was not palpable. Liver function studies are shown in Table 2. The liver biopsy on Feb. 6, 1948, revealed extensive portal cirrhosis. From Feb. 8, 1948, to Feb. 14, 1948, he was given 700 gm. of salt poor albumin in dosages of 100 gm. daily. After the first 200 gm. had been given fever up to 103° was noted every day until Feb. 22. No diuresis was observed. His face was suffused and his skin

most of which had occurred in the previous 2 months. Physical examination revealed a beefy red tongue and icteric sclerae. The liver was not palpable. Pretibial edema of a mild degree was present. Liver biopsy revealed marked evidence of hepatitis and cirrhosis. Her liver function studies are shown in Table 2. From Feb. 22, 1948, to March 13, 1948, she was given a liver diet supplemented with intravenous and oral glucose. From March 13 to April 19 an enriched milk mixture was added to this regime. No significant improvement was observed and ascites developed.

From April 19 to April 30, 1948, a total of 300 gm. of salt poor human albumin was administered. Fever was noted following each injection. Dyspnea was also observed after the last several injections. No diuresis occurred. The patient's condition became progressively worse. She expired on May 8, 1948. The various features of this case were similar in many respects to those recently studied in Denmark.<sup>8,11</sup>

CASE 6. D. M., a 33 year old white male school teacher, was admitted to the hospital on Feb. 3, 1948. He complained of jaundice, dark urine, light stools, ankle edema, and

From Feb. 10 to Feb. 18, 1948, he was given 1000 gm. of salt poor albumin intravenously. During this time he showed no significant changes in his liver function studies. No diuresis was observed. Fever up to 103.6° was noted during the administration of the albumin. His respiratory rate was increased. No immediate beneficial effect was observed from this therapy. Table 2 includes a summary of his liver function studies prior to and after the administration of salt poor human albumin. About 2 months later the jaundice commenced to lessen and by the first of June, 1948, had entirely disappeared.

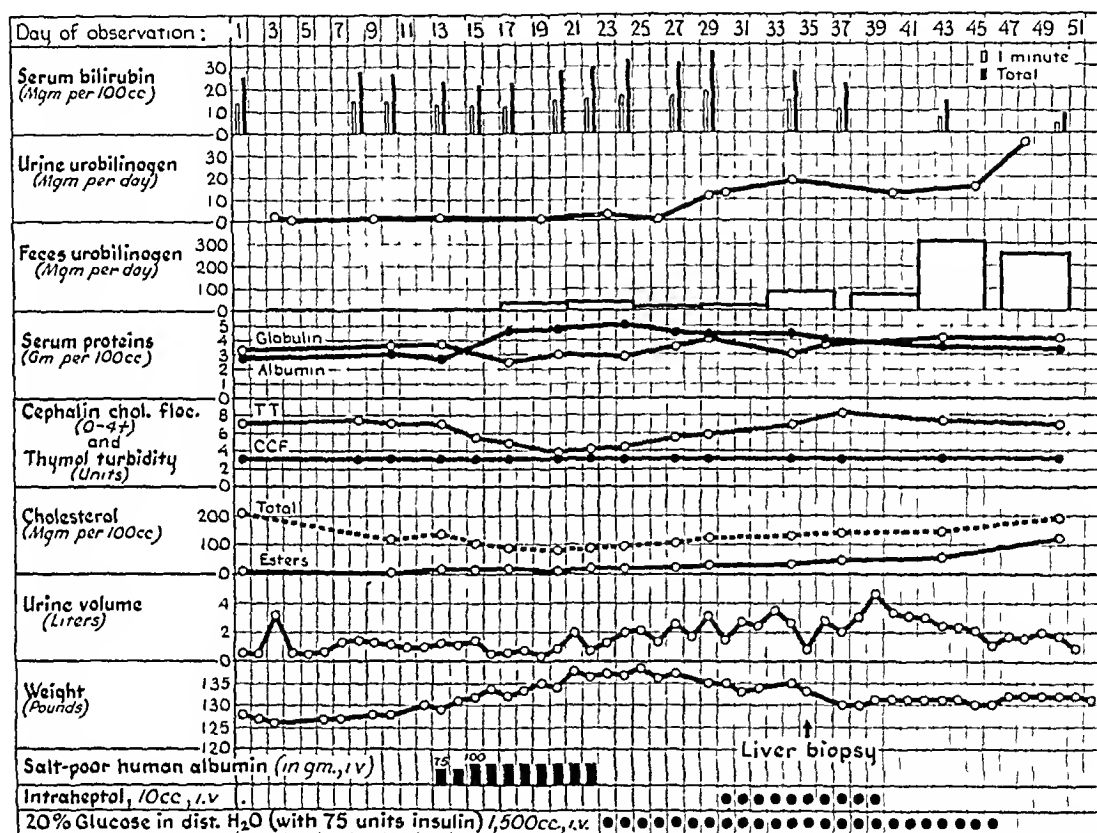


FIG. 2.—Serial liver function studies and other observations in Case 2 (O. S., female, age 42).

bleeding from the gums. He had first noticed these symptoms in March, 1947. At that time he had lost about 25 pounds in weight. After about 3 months the jaundice almost disappeared and he felt fairly well except that he did not regain the weight he had lost nor did he regain his usual vigor. In November, 1947, his symptoms recurred and became progressively worse until the time of admission. Physical examination revealed intense icterus, numerous excoriations, spider nevi, and ankle edema. His liver was palpable 12 cm. below the right costal margin. A liver biopsy revealed hepatitis and distinct, early cirrhosis.

The patient now feels quite well and has resumed his occupation.

**Comment.** The above cases fail to prove any significant value of salt poor human albumin in cases of hepatitis and, or, cirrhosis. On the other hand, the possibility exists that the material may be of considerable value in certain cases. This is at least suggested in Cases 1 and 2 of the present group. In the former, however, there is a likeli-

hood of a coincidental, spontaneous improvement, and in the latter, the improvement, while dramatic and following shortly upon the albumin therapy, did not begin until hypertonic glucose had been administered in considerable amount. One must consider the possibility in this instance that the latter would not have been helpful without the previous replenishment of nitrogen which the albumin undoubtedly effected. It is also possible that the improvement was entirely due to the albumin, as evidence of delayed benefit has been reported previously.<sup>4,9</sup> Thus Eckhardt and co-workers<sup>1</sup> have shown that albumin given intravenously in normal human subjects is rather slowly but completely metabolized, giving rise to a markedly positive nitrogen balance.

While the present study thus fails to decide as to the value of salt poor albumin in the treatment of liver disease, it emphasizes certain dangers attendant on its use and is instructive with respect to certain aspects of renal function in cases of cirrhosis.

It is quite clear from the present cases, that fever and retention of water may be anticipated when salt poor human albumin is given to patients with cirrhosis in the amounts which have been thought to be necessary.<sup>9</sup> The administration of salt poor human albumin has recently been shown by Cargill<sup>2</sup> to increase glomerular filtration and renal blood flow in normal and nephrotic individuals. Cases of hepatic disease were not included. The present study emphasizes that the water retention and increased plasma volume in such cases may result in serious and even fatal pulmonary edema. The remarkable feature of the

water retention in the present cases was that no diuresis occurred in spite of elevation of the serum albumin to high normal or above normal levels, and in spite of significant increases of plasma volume. Rather, there was even a distinct tendency to oliguria. Since there was no lowering of blood pressure nor evidence of other factors which might reduce renal blood flow, the possibility of augmented antidiuretic activity must be considered. In this connection the observations of Ralli and her associates<sup>13</sup> are of particular interest, since they offer objective evidence of an increased concentration of antidiuretic substances in the urines of cases of cirrhosis with ascites.

**Summary and Conclusions.** 1. In 6 cases of hepatitis and, or, cirrhosis of the liver, the administration of salt poor human albumin in large amounts failed to provide decisive information as to its possible therapeutic value. In 2 of the cases dramatic improvement ensued, but in both there was reason to believe that other factors were of greater significance. In the remaining 4 there was neither subjective nor objective evidence of improvement.

2. Fever and water retention were commonly encountered. The latter repeatedly resulted in pulmonary edema, with a fatal outcome in one instance. It was remarkable that coincident with an elevation of the serum albumin to 5 gm. per 100 cc. or higher, the plasma volume and body weight increased, often with signs of pulmonary edema, yet there was no diuresis, in fact the urine volume tended to diminish. The possibility is considered that this lack of diuresis was due to antidiuretic activity such as reported in cases of cirrhosis by Ralli and associates.

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# PROZONE PHENOMENON IN THE SERODIAGNOSIS OF SYPHILIS

## A Clinical Study

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DURING the past several years considerable interest has been shown in the false positive reactions occurring in the serodiagnosis of syphilis. Less attention, however, has been given to the cases of untreated active syphilis in which serological tests were reported as negative. This has led to diagnostic confusion and failure to apply effective therapeutic procedures. Survey of the literature fails to reveal any significant clinical investigations relevant to this problem. The purpose of this report is to bring attention to this potentially important source of diagnostic error.

It is well known that serological tests may be negative in certain types of syphilis. These include early or congenital syphilis, treated cases, and certain forms of cardiovascular and cerebrospinal syphilis. In addition, there remain those whose sera are negative until diluted. These fall into the group manifesting the prozone (prezone or zone) phenomenon as illustrated by the 5 cases described in this paper.

Bacteriologists have long recognized the fact that varying reactivity could be noted in different antigen-antibody ratios. Early in the study of immunology it was observed that some sera which would agglutinate bacteria in high

dilutions would fail to agglutinate when they were mixed with the bacteria in concentration.<sup>13</sup> Ehrlich, as cited by Zinsser and Bayne-Jones, designated this ratio where agglutination failed to occur as "the proagglutinoid zone." Eisenberg and Volk<sup>4</sup> were the first to study the phenomenon in detail, theorizing as to its cause on the basis of Ehrlich's conception of agglutinin structure. In 1926, Dean and Webb<sup>10</sup> investigated the character of the various zones occurring in precipitation reactions, designating the zone of maximal flocculation as the optimal proportion or ratio. Weiner,<sup>11</sup> in his studies in 1937 on the Kline test for syphilis, found sera which, though giving a weak reaction on the direct test, became more distinct on dilution. Subsequently, it was noted that a negative Kline exclusion or Kahn presumptive test does not exclude the possibility of a positive reaction by other technics.<sup>3</sup> Some syphilitic sera are detected only by a less sensitive procedure. Contradictory results are particularly common when both a flocculation and a complement fixation test are used, the former being peculiarly susceptible to zone reactions. Stowe<sup>9</sup> observed the occurrence of negative (prozone) Hinton

reactions in 4 patients, demonstrating that the more sensitive the flocculation test, the more susceptible it is to prozone reactions. Wiener<sup>12</sup> reported in 1940 on the United States Public Health Service investigation by 15 laboratories of the various serological tests for syphilis on 213 known syphilitic sera. Seven sera were found to be falsely negative by two or more laboratories. As the number of units of reagin increased, so did the uniformity of results except for prozone reactions occurring in the Hinton tests. Myers and Perry<sup>8</sup> pointed out that despite the fact that serologists were acquainted with the prozone phenomenon, many laboratories, using one or more of the more recently developed flocculation tests, could readily fail to detect a prozone reaction.

Kahn,<sup>7</sup> in his observations on the "optimal zone reaction" found that certain of the so-called seronegative syphilitic sera became positive when more antigen-antibody ratios were employed. The standard Kahn test employs serum: antigen ratios of 3:1, 6:1, and 12:1. When ratios ranging from 1:1 to 1:100 were employed, positive results were obtained in syphilitic sera which were negative according to the standard Kahn method. Kahn believed that each individual serum has an optimum zone of reactivity, and that negative readings are due to disproportionate amounts of antibody and antigen. A serological pattern common in late syphilis is a negative reaction for standard Kahn and high serum:antigen ratios of 24:1 to 100:1, but a positive reaction in low serum:antigen ratios of 1:1 and 1:2.

**INCIDENCE.** The occurrence of zone effects in the Kline and Hinton tests, according to Greene and Breazeale,<sup>5</sup> is only about 1 in 1000 and should therefore not prove a great source of error. Myers and Perry,<sup>8</sup> on the other hand, tested more than 2000 specimens

with negative Kline-exclusion reactions and found zone reactions in 0.3%. If all routine examinations done during that time were included, the incidence became 0.15%. This increased to 1.7% with the inclusion of atypical "doubtful" tests which the authors believed would have been interpreted as negative by many serologists.

**THEORETICAL CONSIDERATIONS.** In flocculation tests 3 zones are found to exist—the zone of antigen excess (or antibody deficiency), the central equivalence zone, and the zone of antigen deficiency (or antibody excess). Reactivity in the first and third zones may be partially inhibited or fail to occur altogether. The optimal zone (that is, the central equivalence zone), may be demonstrated by varying either the antigen or antibody concentrations. In any one system the optimal ratio is not necessarily a fixed value. When the antigen content is fixed and the antibody concentration varies, the optimal ratio will frequently differ from the one obtained when the antibody concentration is constant and the antigen content is the variable. A difference is found also in precipitation and in agglutination reactions. In the former, precipitation is derived largely from the antibody; in the latter, floccules consist mainly of the antigen-carrying material. Several zone phenomena occur also in the complement fixation reactions.<sup>2</sup> Among these, there has been noted one type analogous to the flocculation prozone described above, namely, due to excess antigen or serum. In addition, there are a number of factors peculiar to the use of the sheep cell-amboceptor hemolytic system which contribute to false negativity in the complement-fixation reaction. Zone reactions based on antigen-antibody ratios are not noted in the spinal fluid. The conventional zone reaction occurring in the colloidal gold test on spinal fluid or its many modifications has been

shown to depend on the concentration and ratio of albumin to globulin. Here the albumin tends to prevent flocculation and the globulin to further it.

**CLINICAL FORMS OF SYPHILIS.** A correlation between the frequency of the prozone phenomenon and the various forms of syphilis has not been established, but it appears to occur predominantly in the late forms of active syp-

condyloma lata. In the 6 cases of Myers and Perry,<sup>8</sup> the clinical diagnosis was mentioned only in two. One patient had far-advanced general paresis and the other acute syphilitic periostitis of the leg and "cardiac symptoms." In the only report of the prozone phenomenon in early syphilis, Callaway<sup>1</sup> found negative or doubtful serologic tests in "many patients" with secondary

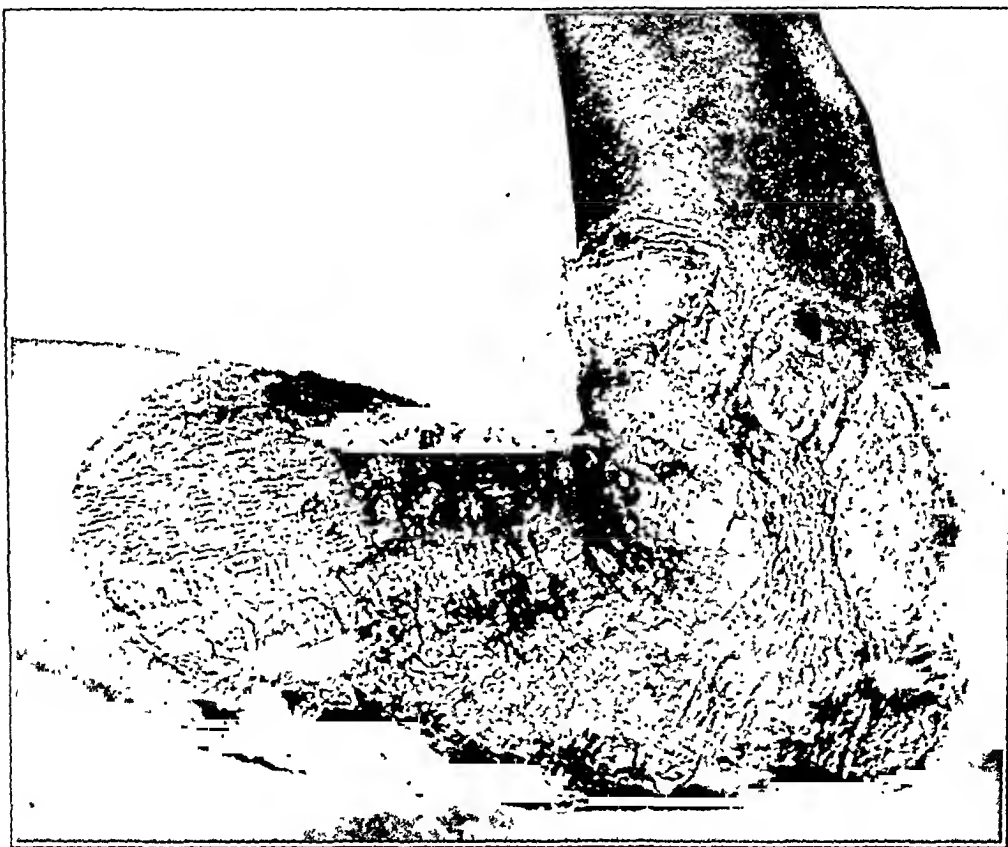


FIG. 1.—Case M. H.

philis. The reports in the literature are concerned almost exclusively with the serological aspects of zone reactions. Heyman<sup>2</sup> reported 1 case with the diagnosis of latent syphilis and simple gastritis. Stowe<sup>3</sup> found 4 cases with prozone reactions (Hinton tests only, the Kahn and Kline tests being positive); 3 had cerebral syphilis and the fourth

syphilis; the quantitative tests showed titers as high as 512 Kahn units.

The following cases illustrate the prozone phenomenon observed by the authors on the teaching service of a large municipal hospital.

**Case Abstracts.** CASE 1. M. H., a 50 year old colored housewife, was admitted to Gallinger Municipal Hospital on August 23,

1945, with hoarseness and dyspnea of 4 weeks' duration, followed by a productive cough, weight loss, weakness, and fever. One year previous she noted a small, nodular, painless, and non-pruritic lesion on her right arm. It increased in size progressively, became reddened, scaly, and ulcerated. One month before admission, a similar area appeared on

strongly suggestive of leprosy. Over the right supra-orbital ridge, a discrete nodule approximately 2 by 3 cm. was present. Later it increased in size and ulcerated, as shown in Fig. 2. Such nodules could be distinguished in the periphery of the face and arm lesions, coalescing to form large areas of destruction and marked scarring. No other significant



FIG. 2.—Case M. H.

the right cheek, spreading over the nose and down the neck; later another nodule appeared on the forehead.

On admission she was moderately dyspneic, with a temperature of 102.4° F. A large, scaly, plaque-like lesion extended over the right antecubital space and arm for approximately 20 cm. (Fig. 1). Similar lesions were noted on the left malar region, nose and neck. Facial lesions were markedly hypertrophic with enlargement and distortion of the nose, resulting in a leonine appearance

findings were present except hoarseness and coarse rales at the base of the left lung posteriorly. Neurological examination revealed no sensory changes.

*Laboratory examinations:* Hemoglobin ranged from 8.57 gm. to 10.5 gm. per 100 cc.; red blood cells from 3,900,000 to 4,500,000 per cu. mm. The leukocyte count on admission was 10,000 but later fell to 4,500 per cu. mm. with a normal differential at all times. Urinalysis was essentially nega-

tive. The corrected sedimentation rate was 0.35 mm. per min. (Rourke-Ernstene). The serum proteins were 7.22 gm. per 100 cc. of blood with the albumin 4.16 gm. and the globulin 3.06 gm. Twenty-four hour sputum specimens were negative for acid-fast bacilli on 15 occasions; gastric washings on 4 occasions. Two cultures from the lesions were

protein was 38 mg. per 100 cc. and the colloid gold curve was 0002100000.

*Roentgenogram* of the chest on October 8 revealed mottling and fibrotic changes at the base of the left lung which were unchanged on December 4. Roentgenogram of the hands revealed no evidence of sarcoidosis. Direct laryngoscopic examination on September 18



FIG. 3.—Case F. Y.

negative for fungi and scrapings of the nasal mucosa were negative for *Mycobacterium leprae*. The tuberculin test (P.P.D.) was negative in two strengths.

*Serological studies* were as follows. The Kahn test was doubtfully positive on August 24, 1945, negative on August 29, positive on September 24, and negative on October 10. The quantitative Kahn on October 12 was 1:16 in a dilution of 1:2048. The spinal fluid

revealed marked edema of the larynx making it difficult to visualize the vocal cords. On October 30, some improvement in the edema was noted but a bronchoscopic examination was deemed inadvisable at the time. Biopsy of the skin lesions on September 8 was interpreted as showing a chronic inflammatory process.

*Course:* The patient became asymptomatic

24 hours following admission except for hoarseness and the cutaneous lesions, the latter progressing despite local therapy. On November 5, bismuth subsalicylate was begun with immediate and dramatic improvement, healing of the skin lesions occurring centrally. Penicillin, 20,000 units intramuscularly every 2 hours, was given from November 14 to the date of her requested discharge on December 8, 1945. She received a total of 6 cc. of bismuth and approximately 6,000,000 units of penicillin. On discharge, the skin lesions had cleared completely. The hoarseness, which had remained unimproved for several weeks, disappeared just prior to her departure from the hospital. The patient failed to return for bronchoscopy, and the etiology of the pulmonary lesion, radiographically unchanged at the time of discharge, was not ascertained. The possibility of syphilitic involvement of the larynx or lungs could not be excluded with certainty. When seen at her home in April, 1947, the patient stated that she had been entirely asymptomatic since leaving the hospital. The sites of the cutaneous lesions were marked only by hyperpigmentation and minimal scarring. Further examination was refused except for a serologic re-check which was 4 plus in a dilution of 1:256. The diagnosis was cutaneous ulcerative gummata with prozone phenomenon.

CASE 2. F. Y., a 71 year old colored male, was admitted to Gallinger Municipal Hospital on March 5, 1947, complaining of chronic ulcers on both legs for 2 years, undiagnosed as to cause and not benefited by attendance at several dermatologic clinics. Increasing dyspnea on exertion had been noted the past year. Approximately 50 years ago he had received local treatment for a penile ulcer.

On admission the systolic blood pressure was 155, the diastolic 65. He was in congestive heart failure with regular rhythm and cardiomegaly with a systolic and diastolic aortic murmur. On the moderately edematous lower extremities, undermining ulcers were present with a striking hyperkeratosis of the surrounding skin (Fig. 3). The ulcers were covered with a grayish-white, foul exudate. Routine laboratory procedures were non-contributory. Cultures from the lesions revealed no significant bacteria or fungi, and biopsy was interpreted as chronic granuloma. The qualitative Kahn test was negative.

The ulcers failed to improve despite vigorous local therapy and restoration of cardiac compensation. Because the diagnostic problem was similar to the first case, a quantitative Kahn test was obtained. It was positive in a titre of 1:2048. The complement fixation test at this time also was positive. Bismuth subsalicylate was administered for 3

weeks followed by 10,000,000 units of penicillin. Healing occurred with residual atrophic scars following bismuth and penicillin therapy; he was discharged to the outpatient department. In view of the persistent high titre, (1:512) 5 months later he received an additional 6,000,000 units of penicillin. The quantitative titre then decreased to 1:256 and the originally negative qualitative Kahn was now a 2 plus positive. The diagnosis was gummatous ulcerations of the legs, syphilitic heart disease with aortitis and aortic insufficiency, and prozone phenomenon.

CASE 3. M. S., a 63 year old colored female, was admitted to Gallinger Municipal Hospital on April 8, 1947, complaining of a draining breast abscess since August, 1946. Biopsy during a prior hospitalization elsewhere in February revealed chronic suppurative mastitis. Therapy, including irradiation, was ineffective and she left the hospital with the breast lesion unhealed and draining. She was bedridden at home until the development of a decubitus ulcer prompted rehospitalization.

She was afebrile on admission. Examination revealed a chronically ill, poorly nourished female with a large decubitus ulcer over the sacrum. An abscess occupied the upper, outer quadrant of the right breast. Multiple sinuses with a serosanguinous discharge were present. Centrally there was deep ulceration with a malodorous, purulent material covering the base. There was no induration of the breast tissue and no regional lymph node enlargement.

The hemoglobin was 12.8 gm. per 100 cc., the erythrocyte count was 2,840,000 per cu. mm., and the leukocyte count was 9200 per cu. mm. with 90% neutrophils. The corrected sedimentation rate was 46 mm. per hour (Wintrobe method). Culture from the breast lesions revealed *Staphylococcus aureus*, streptococci, proteus, and *E. coli*. No fungi could be cultured. Studies for acid-fast organisms including gastric washings were negative. Numerous determinations of serum proteins ranged from 5.04 gm. to 8.60 gm. per 100 cc., but unfortunately the levels were too fluctuant and erratic to be correlated with the clinical course. The albumin-globulin ratio was not disturbed. The initial Kahn and Mazzini tests were reported as doubtful. Subsequent Kahn and Mazzini tests were positive, the former being 2 plus. A quantitative Kahn test was then obtained and was 4 plus in a 1:128 dilution. Skeletal and chest roentgenogram were non-contributory. A biopsy of the breast revealed a subacute inflammatory reaction.

On a high calory and protein diet, intensive parenteral protein therapy, and local care of

the breast lesion and decubitus ulcer, there was no response except for a slight diminution in the amount of discharge from the breast lesion. In view of the positive serologic tests and the patient's failure to respond to therapy she was started May 3 on bismuth subsalicylate, 0.12 gm., twice weekly. Immediate and marked improvement was noted in the breast lesion followed later by granulation of the decubitus ulcer. The patient was discharged June 21, 1947, with both lesions completely healed.

This case illustrates the prozone phenomenon in a patient with a chronic ulcerative breast lesion that healed during the bismuth therapy.

CASE 4. P. B., a 43 year old colored male, was referred to Gallinger Municipal Hospital in April, 1948, by the George Washington University Medical Clinic with a diagnosis of aneurysm of the right subclavian artery. Syphilis was denied and several blood tests during

1:256. The Wassermann test was a 4 plus positive. The patient died suddenly 4 days following admission. Necropsy revealed a syphilitic aortitis; the aneurysm of the ascending aorta had ruptured into the pulmonary artery through the sinus of Valsalva of the posterior aortic cusp. This patient had cardiovascular syphilis with the prozone phenomenon.

Comment. The cases reported here (Table 1) demonstrate the prozone phenomenon as shown by negative or equivocal serological tests which became strongly positive upon dilution of the serum.

In the first case (M. H.), diagnosis was delayed over 7 weeks because of failure to consider the possibility of a prozone phenomenon. Prolonged hos-

TABLE 1.—CLINICAL DATA OF CASES SHOWING THE PROZONE PHENOMENON

Patient	Lesions	Serology		Result of Treatment	
		Qualitative	Quantitative	Clinical	Serological
M.H.	Ulcers of face and arm	Doubtful Negative Positive Negative	1:2048	Cure	1:256
F.Y.	Ulcers of legs and Cardiovascular syphilis	Negative	1:2048	Cure of ulcers	1:256
M.S.	Ulcer of breast	Doubtful	1:128	Cure	—
P.B.	Cardiovascular syphilis	Negative	1:16	Died	—
H.M.	Cardiovascular syphilis	Negative	1:256	Died	—

the past few years had been negative. The systolic blood pressure was 130, the diastolic 70 in both arms. The heart was moderately enlarged. A blowing diastolic murmur was heard at the left sternal border. The qualitative Kahn test was negative, but a quantitative test was 4 plus in a titre of 1:16. Attempted cellophane wrapping confirmed the presence of an aneurysm. This patient with syphilitic heart disease and aneurysm of the subclavian artery also demonstrates the prozone phenomenon.

CASE 5. H. M., a 66 year old white male, was seen in another hospital in June, 1949, in acute left ventricular failure. Examination revealed marked cardiac enlargement, increased supra cardiac dullness, aortic insufficiency and a protodiastolic gallop rhythm. Roentgenogram of the chest revealed a sacular aneurysm of the ascending aorta, cor pulmonale, and pulmonary engorgement. The qualitative Kahn test was negative; the quantitative Kahn test was 4 plus in a dilution of

1:256. The Wassermann test was a 4 plus positive. The patient died suddenly 4 days following admission. Necropsy revealed a syphilitic aortitis; the aneurysm of the ascending aorta had ruptured into the pulmonary artery through the sinus of Valsalva of the posterior aortic cusp. This patient had cardiovascular syphilis with the prozone phenomenon.

pitalization and many expensive diagnostic tests resulted needlessly. The patient was seen by numerous competent internists, dermatologists, syphilologists, and other consultants. The diagnosis of syphilis was not considered due to the marked activity of the lesions and the negative serologic tests. The clinical characteristics of the lesions and their prompt healing under antisypilitic therapy (bismuth) confirmed the serological diagnosis of syphilis which was made eventually.

The appearance of the breast lesion in the third case (M. S.) had been altered by Roentgen-ray therapy, and the clinical features were characteristic of no specific lesion. Vigorous therapy directed at elevation of the depressed

serum proteins may have contributed significantly or solely to the recovery. The erratic reports of the serum proteins, however, make this a difficult factor to evaluate. On the other hand, the definite prozone phenomenon in the Kahn test and the failure to respond to therapy until bismuth was added suggests a syphilitic basis for the breast lesion.

The second, fourth, and fifth cases clearly demonstrate that the prozone phenomenon represents one cause for the negative serologic tests frequently reported in cardiovascular syphilis.

The variability of different serums should keep the clinician constantly alert and suspicious of the serology reported as negative. The routine use of 2 serological tests of different sensitivity or the use of flocculation and complement-fixation tests is highly desirable. Clinical suspicion of a possible syphilitic process should always prompt quantitative studies when routine serological studies are negative or equivocal. The routine use of the quantitative test, although desirable, is not

practical in most laboratories due to the additional work involved.

**Summary and Conclusions.** Five cases of late syphilis with the prozone phenomenon are reported. On the basis of these cases and the investigation of others in this field, it is concluded that due to the prozone phenomenon, negative or doubtfully positive serologic tests do not exclude the presence of late active syphilis.

The prozone phenomenon is not restricted to any particular form or stage of syphilis, occurring in active and latent syphilis, in congenital or acquired forms, in central nervous system, skin, and other types of involvement, but has never been reported in primary syphilis. It is a not uncommon cause of negative serologic tests in cardiovascular syphilis.

Two diagnostic tests of varying sensitivity should be employed routinely in the serodiagnosis of syphilis. If impracticable or if clinical manifestations suggest the possibility of a syphilitic condition despite negative or equivocal tests, quantitative serological tests should be done.

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## RECOVERY FROM UREMIA

A REPORT OF FIVE CASES

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There has been a renewed interest in the phenomenon of acute azotemia not due to acute or chronic nephritis<sup>2,21</sup> and several mechanisms have been advanced to explain the diminished urinary output. It has been suggested that the damage to renal vasculature and parenchyma in anuria following burns,<sup>4</sup> shock,<sup>7</sup> premature placental separation,<sup>20</sup> and crushing trauma<sup>16,22</sup> is due to a circulating toxin and there is experimental evidence that such a toxin may exist in macerated muscle.<sup>3,19</sup> Some cases of sulfonamide poisoning may fall into this group.<sup>13,23</sup> Another mechanism offered to account for anuria or oliguria associated with shock-like states is a diminished renal blood flow and consequent tissue anoxia which depends upon the general fall in arterial blood pressure.<sup>5,9,11,17,21,22,25</sup> That anuria in shock might be the result of a mechanism unrelated to the alteration in circulatory dynamics is indicated by the demonstration of the presence of a humoral antidiuretic substance in subjects in the post-syncope state.<sup>3</sup> A third mechanism is suggested by the experiments of Trueta and others<sup>27</sup> demonstrating reflex nervous constriction of renal cortical circulatory pathways. Stimulation of the proximal ends of severed peripheral nerves resulted in a diversion

of the renal blood flow "wholly or partly from the cortex and short-circuited it through medullary (especially subcortical) blood channels" thereby rendering the cortex ischemic. There has been considerable discussion as to which of these mechanisms is responsible for the acute azotemias occurring under the different circumstances mentioned. The great diversity of anatomical changes, all the way from severe cortical necrosis<sup>11,12</sup> and lower nephron nephrosis<sup>23</sup> to minimal changes in the proximal tubules<sup>1</sup> suggest that one or more of these mechanisms may operate at different times and that no one can adequately explain the findings in all cases. Recently, Bell and Knutson<sup>1</sup> reported 84 cases of azotemia occurring terminally in a variety of conditions in which the kidneys were anatomically normal in all but 20 cases, and these showed only mild to severe hydropic degeneration of the proximal convoluted tubules.

In view of the apparent rarity of recovery from severe degrees of acute azotemia, it seemed important to report 5 cases which, because they survived and subsequently showed adequate renal function, probably represented cases similar to those of Bell and Knutson<sup>1</sup> rather than those with more severe degrees of structural

change. That these 5 cases recovered on vigorous therapy with fluids intravenously and by mouth suggests that dehydration may have affected renal hemodynamics sufficiently to result in acute nitrogen retention.

**Case Reports.** *Case 1.* A 55 year old woman was transferred to Goldwater Memorial Hospital on November 17, 1946, from an institution for indigent homeless because of diarrhea of 3 days' duration. She had been treated with both sulfasuccidine and sulfadiazine without improvement and was sent to the hospital when listlessness and oliguria developed. Her past history was irrelevant except for hypertension and a sudden left hemiplegia at the age of 47.

Physical examination revealed an obese woman who was weak and lethargic and incontinent of urine and feces but who responded when roused. Her skin was dry and her tongue coated. The heart was slightly enlarged to the left and there was a soft apical systolic murmur. Blood pressure was 132/90 mm. of mercury. The abdominal wall was lax and redundant and was slightly edematous. There was minimal edema of ankle and thigh. There was evidence of a residual left hemiplegia with hyper-reflexia. Babinski and Hoffmann signs were present on that side.

On admission, urine examination showed a specific gravity of 1.010 and 1+ albumin. The centrifuged sediment contained a few erythrocytes, 10 to 20 leukocytes and many granular casts per high power field. Sulfonamide crystals were not seen. Culture showed *B. proteus*. Red blood cell count was 4,100,000, leukocytes 10,700 per c.mm.; hemoglobin 13.0 gm. The blood urea nitrogen was 126.4 mg. per 100 cc. and the sulfadiazine level 4.5 mg. Stools were guaiac-positive but negative on culture for pathogens. The chest was clear on Roentgen-ray photography. Electrocardiograms showed prolongation of the Q-T interval, depression of the S-T segment in Leads I, II, and CF<sub>4</sub> and depression of the T wave in leads I and CF<sub>4</sub>.

The impression was that of azotemia due to dehydration and therapy with in-

travenous fluids was initiated. The blood urea nitrogen rose on the following day to 137.5 mg. per 100 cc. but then fell progressively to normal over a period of 9 days. The diarrhea subsided spontaneously during the next several days after admission. The patient became alert. In an electrocardiogram taken after recovery, the Q-T interval had decreased and the other abnormalities had disappeared. Maximum urine specific gravity rose to 1.015 and the urea clearance was established at 68% of normal. The urine cleared gradually and at discharge showed only a trace of albumin and occasional leukocytes.

*Case 2.* A 78 year old Irish male was hospitalized at Goldwater Memorial Hospital on December 10, 1946, because of diarrhea of 6 days' duration which failed to respond to paregoric or sulfadiazine. He grew progressively weaker and became severely dehydrated. Digitalis was given when the blood pressure fell from 170/90 to 115/80 mm. of mercury.

On physical examination, he was disoriented and semicomatose. The skin was dry, the eyeballs soft and the tongue, palate and pharynx coated with a brown deposit. Breath sounds were distant and the chest hyperresonant. The rhythm of the heart was irregular and shown by electrocardiogram to be due to a wandering pacemaker. Blood pressure was 110/60 mm. of mercury. The abdomen was doughy. The radial arteries were markedly sclerotic. The hands and feet were cool and showed a purplish mottling.

On admission, the urine revealed 1+ albumin and on microscopic examination, rare erythrocytes, 3 to 5 leukocytes and occasional casts per high power field. Sulfadiazine crystals were not seen. There was hemoconcentration. Stool cultures were negative for pathogens. Blood urea nitrogen was 154.4 mg. per 100 cc.

The patient was considered to be suffering from azotemia secondary to dehydration and the administration of intravenous fluids consisting of 5% glucose in physiological saline and distilled water was begun. On this regimen, drowsiness lessened and by the 4th day, adequate fluid intake was managed orally. The

diarrhea responded slowly to sulfasuccidine and intravenous fluids but the blood urea nitrogen fell promptly to 18.5 mg. on the 10th hospital day. Digitalis was discontinued and was not further required. Standard urea clearance, shortly after clinical recovery, was 25% of normal and 4 months later rose to 43% of normal. Blood urea nitrogen was 24.5 mg. and urine specific gravity 1.018 at this time.

*Case 3.* The patient, a 74 year old colored female was transferred from another hospital to Goldwater Memorial Hospital on July 7, 1944, because of gangrene of the right big toe. She was a known hypertensive of about 4 years' duration and was fairly well until about 4 months prior to admission when she developed a sore on the right big toe which, in spite of various attempts at therapy, became gangrenous.

Physical examination revealed an elderly colored female in no apparent distress. Arcus senilis was present. The heart was enlarged to the left. There was a systolic murmur at the apex. The abdomen was normal. The right big toe was malodorous and necrotic. The dorsalis pedis and popliteal pulsations were bilaterally absent.

On admission, the urine examination showed a trace of albumin and the specific gravity was 1.011. The blood urea nitrogen was 15.1 mg. Blood Wassermann was negative. The electrocardiogram showed a left deviation of the electrical axis. Roentgen-ray revealed that the heart was enlarged to the left. The aorta was dilated and calcified. Roentgen-ray of the lower extremities showed calcification of vessels and decalcification of bones.

In July, 1944, the patient's right big toe was amputated. The course following the operation was uneventful until a bout of broncho-pneumonia occurred in December, 1945. In January, 1947, the patient was transferred to the medical service because of slowly developing dyspnea, orthopnea, intermittent substernal discomfort, and edema despite the use of digitalis and ammonium chloride. Because edema of lower extremities was marked and congestion of lungs by Roentgen-ray examination, mercuripurin therapy was started. Following rather liberal adminis-

tration of this diuretic, the patient became disoriented and drowsy on February 10, 1947. The tongue and skin were dry. Involuntary twitchings of the muscles of extremities were observed. Blood urea nitrogen was found to be 89.2 mg. per 100 cc., carbon dioxide combining power 30 volumes % and calcium 10.4 mg. per 100 cc. Parenteral fluids were administered by clysis but apparently in insufficient quantity because she became even less responsive, reacting only to painful stimuli. Her abdomen became markedly distended. Three days later (February 13, 1947), blood urea nitrogen was 114 mg. and the carbon dioxide combining power 23 volumes %. Intravenous fluids were then given copiously and the patient began to improve. The blood urea nitrogen fell rapidly to normal values, the carbon dioxide combining power returned to normal and the patient improved greatly. Renal function studies after recovery showed phenolsulfonphthalein excretion of 40% at the end of 2 hours and urea clearance of 53% of normal. Subsequent urinalyses showed specific gravities of 1.010 to 1.012 with a trace of albumin. The patient's renal status has remained unchanged since.

*Case 4.* The patient, a 70 year old Puerto Rican man was transferred from another hospital to Goldwater Memorial Hospital with a diagnosis of hypertensive and arteriosclerotic heart disease and possible cirrhosis of the liver. Patient's history was very difficult to obtain because of his stupor and language difficulty. He was apparently well until about 4 months prior to hospitalization when he began to complain of epigastric pain and occasional bouts of vomiting and noticed loss of weight. Subsequently, he experienced bouts of precordial pain and edema of the ankles. There was no history of dyspnea or orthopnea. Progressively failing vision beginning 4 years prior to admission led to enucleation of the left eye. Otherwise, his past history was uneventful. At the hospital from which he was transferred, the level of creatinine in the blood was said to be 3.5 mg. per 100 cc. and the blood urea nitrogen 105 mg. His blood Kahn was negative.

On admission, the patient appeared acutely ill and semi-stuporous. He showed evidence of weight loss and considerable dehydration. There was no dyspnea or orthopnea. His left eye was enucleated and the right eye showed a corneal opacity. His tongue was dry and coated. His lungs were clear to percussion and auscultation. The heart was enlarged to the left. There was a faint systolic murmur at base and apex. Blood pressure was 150/70 mm. of mercury. There were no abdominal masses palpable. The extremities were not edematous and arterial pulsations were good.

On admission, hemoglobin was found to be 14.0 gm. red blood cell count 7,000,000, white blood cell count 10,800 per c.mm., and hematocrit 56%. The urine showed a specific gravity of 1.009, a trace of albumin and 20 to 30 leukocytes per high power field. The blood urea nitrogen was 98.8 mg. per 100 cc. The total serum protein was 7.8, albumin 4.1 gm. per 100 cc. On the following day, after institution of intravenous fluids, the red blood cell count had fallen to 4,200,000 per c.mm., the hematocrit to 43%. However, the blood urea nitrogen remained elevated (112.3 mg. with a carbon dioxide combining power of 49 volumes %). Total protein was 5.6 gm. per 100 cc. after institution of therapy. The cholesterol was 191 mg. The calcium was 9.2 mg. and the alkaline phosphatase was 11.9 King-Armstrong units. Roentgen-ray photograph of the chest showed a slight accumulation of fluid at the right base. The remainder of the pulmonary field was clear. The heart was enlarged and the aorta somewhat widened and tortuous. The electrocardiogram was essentially normal. The admission impression was hypertensive and arteriosclerotic heart disease. The renal lesion was thought to be chronic glomerulonephritis or chronic pyelonephritis with uremia.

The patient was treated rather vigorously with infusions of glucose in saline and glucose in water and intramuscular penicillin. Although the prognosis was very grave because of semi-coma, Cheyne-Stokes breathing and the high level of urea nitrogen in the blood, the patient

began, gradually but definitely, to improve. Lethargy gave way to alertness and the patient became oriented. The blood urea nitrogen level fell from 112 mg. to normal. The improvement took place during a period of 2 weeks.

Following recovery, investigation showed that the patient had relatively good renal function. The phenolsulfonphthalein excretion was 57% at the end of 2 hours. The urea clearance was 83% of normal. Fishberg concentration test yielded a specific gravity of 1.020. The urine gradually cleared. Further renal studies showed a filtration rate of 76 cc. per minute (normal, 100 to 125 cc. per minute), para-amino hippuric acid clearance of 320 cc. per minute (normal 400 to 600 cc. per minute). The urine flow was 3 to 4 cc. per minute. Retrograde pyelogram was essentially normal. He was discharged to be followed in the out-patient clinic. It was believed that the patient's principal difficulty was dehydration which resulted in prerenal azotemia. The cause of the dehydration was not ascertained.

*Case 5.* The patient, a 56 year old widow, was admitted to Lenox Hill Hospital on April 23, 1947, for possible intestinal obstruction. Her chief complaints were nausea, vomiting, mild dyspnea, and obstipation of 11 days' duration. This was preceded by epigastric pain which persisted for 2 days. She had no bowel movements, but did continue to pass flatus. Vomiting 3 or 4 times a day persisted. The vomitus was bile stained but never fecal in character. In the week prior to admission, she had moderate degree of lower abdominal pain aggravated by motion and became extremely weak.

Ten years ago, she had been told that she had heart disease. One year ago, she began to have ankle edema and exertional dyspnea that became rather marked on climbing one flight of stairs. She was put on digitalis leaf, 0.1 gm. a day, which she continued to take until 2 months prior to admission, when she discontinued the drug.

On physical examination, she was extremely lethargic and acutely ill. Hypertension was marked and a uremic odor

was noted on her breath. Her pupils were equal, round, widely dilated and did not react to light. Eye grounds were essentially normal. The tongue was beefy and dry. A few scattered rales were heard at both lung bases posteriorly. Blood pressure was 100/80 mm. of mercury. Heart sounds were distant and of poor quality. A soft blowing systolic murmur was heard over the entire precordium. Roentgen-ray examination of the heart revealed some enlargement of the left ventricle and calcification and dilation of the arch of the aorta. The electrocardiogram was essentially normal with the exception of slight slurring of the QRS complex and a prolongation of the P-R interval (0.22 sec.). The abdomen was but slightly distended and the liver edge was palpable 1 cm. below the costal margin. There was slight edema of the legs and arms. Reflexes were present but sluggish.

The blood urea nitrogen was found to be 110 mg. per 100 cc. and the carbon dioxide combining power was 22.3 volumes %. Hemoglobin was 12 gm.; red cell count was 4.3 million per c.mm.; leukocytes numbered 16,300 per c.mm. with 87% granulocytes. Plasma chlorides were 584 mg. per 100 cc. (expressed as sodium chloride). Urine was pale yellow with a specific gravity of 1.002. Microscopic examination of the urine revealed only occasional hyaline and granular casts and about 10 white blood cells per high power field.

Thus the patient, who appeared to have an intestinal obstruction, was quite obviously in a state of uremia. The presence of an obstructive lesion also remained a possibility, but in the absence of marked distention and with the persisting passage of flatus, this was thought to be, at most, an incomplete one. Hence the uremia was considered the main problem and she was accordingly given fluids to the extent of 1500 to 2000 cc. daily in the form of glucose in distilled water, at first intravenously, and thereafter by elysis. After an initial saline infusion, further sodium was withheld because of her cardiac status. During periods when she was reactive, she remained mentally confused and disoriented. She showed considerable mus-

cular irritability but had no convulsions. Urine output was quite small for the first 3 days, totalling about 500 cc. Thereafter, it increased and averaged about 800 cc. daily. The urine was poorly concentrated (specific gravity below 1.005) and was negative for albumin. At no time did microscopic examination of the sediment show more than occasional casts, white blood cells and red blood cells.

An episode of acute pulmonary edema occurred on the 5th day of hospitalization for which she was digitalized. Several days later, slow auricular fibrillation (ventricular rate of 90 per minute) was found to be present. The rhythm failed to revert to normal sinus with quinidine. For nearly 2 weeks, she remained in a semi-stuporous state and had no bowel movements. She was, however, taking nothing by mouth and, since she continued to pass flatus and distention did not develop, she was not thought to be obstructed. Blood urea nitrogen had risen by the 11th hospital day to 153 mg. per 100 cc. Muscular twitching became marked and a loud pericardial friction rub developed. Then, during the next few days, she began to improve symptomatically, became more alert and oriented and took small amounts of fluid by mouth. The muscular irritability and pericardial friction rub disappeared. By the 14th hospital day, blood urea nitrogen had dropped to 80 mg. and the carbon dioxide combining power had risen to 32 volumes %. Following this, she progressed rapidly and 2 weeks later, the blood urea nitrogen was 12.5 mg. The clinical picture had shown an equally dramatic improvement.

Urea clearance done at this time was 42% of normal and the maximum urine concentration obtained was a specific gravity of 1.014. It was evident that some impairment of kidney function was present but even assuming that her kidney function was the same before this episode (it may well have been better), it was not in itself sufficiently impaired to have accounted for the development of uremia.

The course was thereafter uneventful. With ingestion of food and fluids, there followed normal bowel function and

TABLE 1. URINE AND BLOOD ANALYSIS VALUES DURING ILLNESS AND AFTER RECOVERY IN 5 CASES OF UREMIA

DURING ILLNESS					AFTER RECOVERY							
URINE			BLOOD		URINE	RENAL FUNCTION TESTS		BLOOD				
Cases	Max. Sp. Grav.	Sediment	Alb.	Max. Urea Nitrogen Mg./100 cc.	CO <sub>2</sub> Comb. Power Vol. %	Max. Sp. Grav.	Sediment	Alb.	PSP Per Cent in 2 hrs.	Urea Clearance Per cent of normal	Urea Nitrogen Mg./100 cc.	CO <sub>2</sub> Combining Power Vol. %
1	1.010	Few RBC. 10-20 WBC. Many granular casts.	+	137.5		1.015	Normal	Tr.		68	14.0	78.0
2	1.015	3-5 WBC. Occasional casts	+	154.4		1.018	Normal	0		43	18.5	
3				114.0	23.0	1.012	Normal	Tr.	40	53	9.9	61.0
4	1.009	20-30 WBC.	Tr.	112.3	43.0	1.020	Normal	0	57	83	8.9	53.0
5	1.002	10 WBC. Occasional hyaline and granular casts.	0	153.0	22.3	1.014	Normal	0		42	12.5	



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# ON THE OCCURRENCE OF HERPES ZOSTER IN CARCINOMA OF THE BREAST

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It is common knowledge amongst oncologists and radiotherapists that the incidence of herpes zoster in Hodgkin's disease,<sup>15</sup> leukemia and metastatic carcinoma is greater than in the population at large, although statistics on the subject are not available. On the basis of large surveys, herpes occurs in the proportion of 1 to 2% of all diseases of the skin,<sup>8</sup> while in the period of 1925 to 1935 it was observed in 0.06% of 200,000 admissions to Bellevue Hospital in New York.<sup>9</sup> With the exception of the studies by Pancoast and Pendergrass<sup>15</sup>, and Craver and Haagenson,<sup>5</sup> most previous papers have been concerned with single case reports of herpes zoster in carcinoma and allied diseases. The observance of 16 cases of this disease entity in a survey of 406 cases of carcinoma of the breast, giving an incidence of 4%, prompts this clinical presentation.

Herpes zoster is generally conveniently classified into 2 groups: The idiopathic or primary, and the symptomatic or secondary, forms. The idiopathic herpes occurs in otherwise normal individuals, and characteristically produces a vesicular eruption which follows a zonal or segmental distribution and is accompanied by fever, leukocytosis and marked pain. At times the eruption may be delayed in onset, and the pain may simulate that of a "surgical abdomen". The local skin lesion is self-limited. However,

post-herpetic pain may become a very distressing aftermath which may lead the patient to the radiotherapist if the early lesion has not had the benefit of irradiation.

In 1864, Mitchell, Morehouse and Keen<sup>13</sup> showed that irritation and not section of a nerve was the cause of zoster and similar eruptions. Later, in 1872, Mitchell<sup>12</sup> indicated that at some time in the history of a nerve injury it is common to see certain forms of eruption, which are herpetic, vesicular, or in the shape of bullae.

Head and Campbell<sup>10</sup> in 1900 in an elaborate paper gave a large number of facts regarding the origin and distribution of zoster. They found destructive changes in the posterior ganglia of the spinal cord and in the Gasserian ganglion, and degeneration in the nerves leading to the skin. They concluded that some agent chooses the posterior root ganglion for its selected activity, producing profound inflammatory changes, which in time give rise to the irritation of its nerve elements. In 1902, Van Harlingen<sup>17</sup> reviewed the reports as to the origin and nature of herpes zoster.

The present day conception of the disease regards a filtrable virus as the causative agent. Many workers in the field believe there is a close relationship between the virus of varicella and that of herpes zoster.<sup>1</sup> However, this claim lacks unanimity.<sup>6</sup>

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Secondary or symptomatic herpes has an obscure and mixed etiologic background, having been observed during and following a variety of disease entities. It is seen during the course of many infectious diseases such as pneumonia, influenza, meningitis, and tuberculosis. In addition, it has followed trauma, pressure from a spinal cord tumor,<sup>11</sup> intoxication by poisons, and various neoplastic diseases. Carrière<sup>4</sup> in 1895 reported a case of femoro-cutaneous zoster following cancer of the uterus. Although there was no cancerous infiltration of the nerve, there was parenchymatous neuritis and he thought that the neuritis was due to a local and direct action of cancer toxins. The obscure pathogenesis has prompted numerous reports of unusual inciting agents. Considering the reputed frequency of herpes zoster in cases of cancer, Craver and Haagenson<sup>5</sup> stated that, "it is peculiar that there are not more of these cases on record".

Idiopathic herpes zoster was subjected to careful histologic study on 3 autopsied cases by Denny-Brown and Adams.<sup>7</sup> These workers found degeneration of related motor and sensory roots, severe neuritis, unilateral segmental poliomyelitis, and localized leptomeningitis. They concluded that the phenomena of herpes zoster required more than the ganglionic lesion for their explanation, but depend in part on a poliomyelitis and motor neuritis.

Symptomatic zoster is seen in fairly frequent association with Hodgkin's disease. Pancoast and Pendergrass<sup>15</sup> in 1924 reported 4 cases of herpetiform eruptions in Hodgkin's disease and 1 case in ovarian sarcoma. They thought that herpes zoster occurred much more frequently in malignant conditions than generally was believed. Craver and Haagenson<sup>5</sup> encountered 7 cases of herpes zoster (2.1%), in 329

cases of lymphosarcoma, Hodgkin's disease, and leukemia. To them the clinical data suggested that the herpes zoster was due to involvement of the nervous structures by the tumor process. Barton and O'Leary,<sup>3</sup> who were able to demonstrate a leukemic infiltrate in the zosteriform lesion in a case of generalized herpes zoster, regarded the herpetic lesion as merely the "traumatic stimulus" which caused an influx of leukemic infiltrate into the affected site. Sometimes the zosteriform infiltrate is noted as late as 6 months after the appearance of herpes zoster.<sup>2</sup>

The existence of a symptomatic type of herpes zoster brought on by tumor metastases is denied by some investigators. Mumme<sup>14</sup> autopsied a case in which herpes zoster developed in the territory of the 11th and 12th thoracic and 1st and 2nd lumbar ganglia in a patient afflicted with metastatic seminoma of the 12th thoracic vertebra. The 12th thoracic spinal ganglion was shown histologically to be entirely destroyed by tumor masses which contained within them inflammatory infiltrates. The 11th thoracic and 1st and 2nd lumbar spinal ganglia were completely free of metastatic seminoma, but exhibited a non-suppurative spotty inflammation with plasma cells indicating a true ganglionitis. Mumme denies a symptomatic zoster because there was no chronological relationship between the destruction of the 12th spinal ganglion and the appearance of the herpes zoster, although the conclusion about the time relationship is not very clear from the case history. In addition, the zoster did not limit itself to the territory supplied by the 12th thoracic ganglion, but extended also to include the 3 adjacent vertebrae. The inflammatory changes which in greater or lesser degree were present in all 4 spinal ganglia presented exactly the same histological picture as those

TABLE I.--DATA ON 16 CASES OF HERPES ZOSTER AND CARCINOMA OF THE BREAST

Case No.	Age	Date of Mastectomy	Post-op. Roentgen Therapy	Date of Appearance of Zoster	Side Involved and Segments	Site of Metastases	Date of Appearance of Metastases	Date of Death
1	37	4/29/37	x	?	homolateral; segments?	T6 L2	5/6/40 1/13/42	8/7/43
2	42	9/10/36	x	9/15/37	homolateral; L1 distribution	T9, 12, and L2	3/16/37	Sept. 1939
3	49	4/28/37	x	July 1937	?	cervical, supraclavicular, liver, lungs, pelvis, legs	9/18/38	unknown
4	35	12/22/34	0	?	homolateral; segments?	C2, T9, 11, 12 iliac	11/2/35	10/22/36
5	71	none	0	7/11/38	homolateral, T4 and 5	T5	8/3/38	June 1939
6	60	6/16/39	0	1/22/43	homolateral; segments?	bilateral pleural metastases	1/22/43	7/27/43
7	43	1/3/33	x	?	homolateral; T7 and 9	skin, liver, axilla	9/22/33	12/14/33
8	45	4/19/35	x	10/28/36	contralateral; segments?	lungs	1/8/37	April 1937
9	57	11/15/32	x	May 1934	homolateral; segments?	brain	at death	April 1935
10	45	May 1933	x	4/28/36	?	lung, opposite breast	10/30/36	unknown
11	75	May 1932	0		homolateral; segments?	ant. mammary nodes	1/3/34	3/22/35
12	75	10/1/36	0	3/24/37	homolateral; segments?	?	at death	9/21/38
13	74	5/15/35	x	9/26/38	contralateral; facial	none	—	alive on 12/6/44
14	64	11/15/32	x	6/8/34	homolateral; segments?	none	—	11/17/41; cerebral hemorrhage
15	49	8/12/22	x	5/20/33	homolateral; segments?	none	—	alive on 4/26/45
16	74	8/1/37	x	3/7/38	contralateral; segments?	none		alive on 4/1/45

customarily found in zoster of virus etiology. The seminoma metastases, in Mumme's opinion, merely acted as a predisposing factor to the invasion of the virus and the appearance of the disease.

Wohlwill<sup>18</sup> expressed a similar opinion concerning etiology as a result of his histological study. He found the involvement of the spinal ganglia was not constant either in the idiopathic or secondary type. While the dorsal ganglion was most frequently the site of involvement, the findings suggested that it could be produced by involvement of any point in the afferent portion of the reflex arc.

*Clinical Material.* The records of 406 cases of carcinoma of the breast seen by us at this hospital from 1932 to 1939 were investigated to complete previous studies at this institution on this subject.<sup>16</sup> Sixteen cases of herpes zoster were encountered, in 12 of whom there was evidence of metastatic disease either before or after the appearance of the cutaneous disease. The remaining 4 cases survived between 6 and 12 years after the herpetic attack with no evidence of metastatic malignancy.

*Case Abstracts.* CASE 1. S.S., a 37 year old white female, had a left radical mastectomy performed April 29, 1937 for a mass observed 4 weeks earlier. The pathologist reported a "scirrhous carcinoma with metastases to axillary nodes." Received postoperative irradiation to involved side beginning May 8, 1937. Recurrences in scar removed May 1939 and September 1939. Metastases to left axilla and 6th thoracic vertebra appeared May 6, 1940, to left upper lobe on Sept. 12, 1940, and 2nd lumbar vertebra on Jan. 13, 1942. Herpes zoster also appeared, but date and distribution not stated. Died Aug. 7, 1943.

CASE 2. J.H., a 42 year old white female, had a left simple mastectomy performed Sept. 10, 1936 for a mass present 18 months. Received preoperative and postoperative Roentgen therapy, the latter including the opposite breast beginning Oct. 8, 1936. Pathologist reported "adenocarcinoma." On March 16, 1937 developed metastases to right ilium, 9th and 12th thoracic, and 2nd lumbar vertebra. Herpes zoster involving the left 1st lumbar

distribution appeared Sept. 15, 1937. The sacrum, coccyx, and right acetabulum revealed metastases on Nov. 26, 1937. Died September 1939.

CASE 3. G.D., a 49 year old white female, had a left simple palliative mastectomy performed April 28, 1937 for a mass present for 11 months, together with supraclavicular adenopathy and skin nodules. Pathologist reported "adenocarcinoma." Received preoperative and postoperative Roentgen therapy, the latter including the opposite breast. Herpes zoster appeared in July 1937. Segments involved not reported. Generalized metastases on Sept. 17, 1938. Alive with malignancy when last seen on Dec. 17, 1938.

CASE 4. E.M., a 35 year old white female, had a right radical mastectomy performed Dec. 22, 1934 for a mass present 1 month. Pathologist reported "carcinoma with metastases to axillary nodes." Pre-operative Roentgen-ray therapy administered. Metastases noted in right ilium on Nov. 15, 1934, the 9th, 11th, and 12th thoracic vertebrae on November 2, 1935, and the odontoid on Aug. 29, 1936. Herpes zoster appeared on right side. Date and segments involved not stated. Died Oct. 22, 1936.

CASE 5. I. W. F., a 71 year old white female who was seen elsewhere for a mass in the right breast. No operation was performed, but Roentgen-ray therapy of unknown amount and factors was administered. Developed herpes zoster involving right 4th and 5th thoracic segments. Roentgen examination on Aug. 3, 1938 revealed metastatic disease involving the 5th thoracic vertebra. Died June 1939.

CASE 6. M. L., a 60 year old white female, had a left radical mastectomy performed June 16, 1939 for a mass which had been present for 2 years. The axilla was not completely dissected. Pathologist reported "adenocarcinoma with metastases to axillary nodes." No postoperative irradiation was administered. On Jan. 15, 1940, metastases developed in the left axilla and supraclavicular areas. On Sept. 8, 1942, metastases appeared in left internal mammary nodes and right breast. On Jan. 22, 1943, a bilateral pleural effusion and herpes zoster on the left side appeared. Segments involved by herpes not stated. Died July 27, 1943.

CASE 7. C.V., a 43 year old white female, had a right radical mastectomy performed Jan. 13, 1933 for a mass present 1 year. Pathologist reported "carcinoma with metastases to axillary nodes." Received postoperative Roentgen-ray therapy, including opposite breast. On Sept. 23, 1933, developed metastases to skin, right axilla, and possibly liver. Herpes zoster

involving right 7th and 9th intercostal nerves appeared, but date not noted. Died Dec. 14, 1933.

CASE 8. R. T., a 45 year old white female, had a left radical and right simple mastectomy performed on April 19, 1935. Pathologist reported "carcinoma of left breast with lymph node metastases." Postoperative Roentgen therapy administered to both sides of chest beginning May 20, 1935. Herpes zoster appeared on left side on Oct. 28, 1936. Segments involved not stated. Pulmonary metastases noted Jan. 8, 1937. Died April 1937.

CASE 9. C. G., a 57 year old white female, had a right radical mastectomy performed elsewhere on Nov. 15, 1932 for a mass present for 6 months. Pathologist reported "medullary carcinoma." Postoperative Roentgen therapy administered to both sides of chest beginning Jan. 4, 1933. Herpes zoster noted on right side in May 1934. Segments involved not stated. Died April 1935 with evidence of cerebral metastases.

CASE 10. W. H. B., a 45 year old white female, had a right radical mastectomy performed elsewhere in May 1935 for a mass that had been present for 8 months. The pathological report was not available. Postoperative Roentgen-ray therapy was administered to both sides of the chest. Pulmonary metastases and recurrence in the scar appeared on Aug. 8, 1935. Herpes zoster was noted on April 28, 1936, the location and distribution being unspecified. Metastases appeared in the left breast on Oct. 30, 1936. Patient was last seen alive with malignancy on Oct. 30, 1936.

CASE 11. L. J. H., a 75 year old white female, had a right radical mastectomy performed elsewhere in May 1932 for a mass present for 15 months. Postoperative Roentgen-ray therapy was not administered. A recurrence developed in the scar in February 1933. Herpes zoster appeared on the right chest on Sept. 6, 1933. Segments involved not stated. Internal mammary node metastases were noted on Jan. 3, 1934. Patient died March 22, 1935.

CASE 12. E. L., a 75 year old white female, had a right radical mastectomy on Oct. 1, 1936 for a mass which had been present for 5 years. Pathologist reported "adenocarcinoma with lymph node metastases." Postoperative Roentgen therapy begun Nov. 4, 1936. Herpes zoster developed on right thoracic wall on March 24, 1937. Segments involved not stated. Died Sept. 21, 1938 with malignancy.

CASE 13. R. S., a 74 year old white female, had a left simple mastectomy performed on May 15, 1935 for a mass present for several months. Pathologist reported "duct type of

adenocarcinoma." Received postoperative Roentgen therapy, including opposite breast. Developed right herpes zoster facialis on Sept. 26, 1938. Alive and well on Dec. 6, 1944.

CASE 14. D. A. H., a 64 year old white female, had a left radical mastectomy performed Nov. 15, 1932 for a mass present 3 months. Pathologist reported "scirrhous carcinoma." Postoperative Roentgen therapy to both sides of chest and left axilla begun Feb. 21, 1933. Developed herpes zoster on left side on June 8, 1934. Segments involved not stated. Died Nov. 17, 1941 of cerebral hemorrhage with no clinical evidence of metastatic disease.

CASE 15. J. S., a 49 year old white female, had a left radical mastectomy performed on Aug. 12, 1932 for a lump which had been present 3 weeks. Pathologist reported "scirrhous carcinoma." Both sides of chest and left axilla were irradiated beginning Sept. 12, 1932. On Jan. 25, 1933 changes were observed in left lung which were believed to represent possible radiation fibrosis. On May 20, 1933 patient developed herpes zoster on left side. Segments involved not stated. Alive and well on April 26, 1945.

CASE 16. W. R. T., a 74 year old white female, had a right simple mastectomy performed elsewhere on Aug. 1, 1937. Histologic examination revealed adenocarcinoma. Postoperative Roentgen therapy begun Feb. 28, 1938 to right breast and axillary region. Developed herpes zoster on March 7, 1938 on left side. Segments involved not stated. Alive and well on April 1, 1945.

**Comment.** Fourteen of the patients with herpes received preoperative or postoperative irradiation with Roentgen rays, or both, only 2 receiving no irradiation. All 4 of the patients who developed herpes without metastatic disease were subjected to irradiation. Of the latter 4, one developed facial herpes 39 months after irradiation of the breast and its lymphatic areas, whereas the other 3 developed thoracic herpes 40, 8, and 1 month respectively after irradiation. In view of the multiplicity of inciting agents, the possible etiologic rôle of irradiation must also be considered, although it is difficult to comprehend the significance of thoracic radiation in the production of facial herpes. In the 10 cases develop-

ing metastases who had postoperative irradiation, the possible etiologic rôles of both factors are to be considered. In only 6 of these cases was it possible to determine the time interval from irradiation to appearance of herpes, the figures ranging from 4 to 40 months.

Twelve of the cases of herpes developed evidence of metastatic disease either before or after the appearance of the eruption. Eleven of these cases had some type of breast operation performed. Of 350 cases operated upon, 218 (62%) subsequently showed evidence of recurrent or metastatic disease. Thus, the incidence of herpes zoster in metastatic disease was 11 cases in 218 (5.0%), while the incidence in those cases not showing metastatic disease was 4 cases in 132 (3.0%). Of 56 cases of breast carcinoma not subjected to surgery because of one or more contraindications, only 1 developed herpes zoster, and this case showed metastases.

The presence of metastatic disease was manifested clinically by supraclavicular nodes, cutaneous nodules, or rarely cerebral symptoms, while in others there was Roentgen evidence of pulmonary or bony involvement. All of these cases died at home, and unfortunately no autopsy studies are available. However, it is hoped that by calling attention to the relatively high incidence of herpes zoster in carcinoma of

the breast this association will be noted more carefully in the future, and careful clinico-pathologic studies, particularly including that of the spinal cord, may reveal the etiological factors. Too often the lesions of herpes zoster are noted merely in passing, with no attention directed to the dermatomes involved and possible relationship to underlying neoplastic or inflammatory process.

Past evidence indicates that the metastatic disease merely prepares the soil (*terrain maladif*) for the invasion of the virus or causative agent of herpes zoster, rather than actually causing the disease itself. In some cases, knowledge of the association of herpes zoster and malignancy may aid in the uncovering of an otherwise cryptic neoplasm or unsuspected leukemia, although diagnosis rarely is a problem in breast carcinoma. All patients with herpes zoster should be subjected to a careful clinical study for possible neoplastic disease.

**Summary.** Herpes zoster occurs in relatively high incidence in carcinoma of the breast, especially in those cases showing metastatic disease.

Most of the patients developing herpes had been subjected to Roentgen radiation; the etiologic significance of radiation and metastases has not yet been clarified.

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# PROGRESS OF MEDICAL SCIENCE

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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## CURRENT TRENDS IN DIAGNOSIS AND TREATMENT OF CERVICAL CANCER

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RECENT years have witnessed a notable improvement in the diagnosis of early cervical cancer. A new disease entity<sup>69,77</sup>, "noninvasive carcinoma" or "carcinoma in situ", has been established as the earliest known type of cervical cancer, and its detection has been made possible through the refinement of existing diagnostic techniques. These developments may be expected to produce a significant decrease in the 17,000 deaths caused annually by cervical carcinoma. Results of treatment have repeatedly shown that either irradiation or surgery can cure the majority of early cervical cancers; that neither can cure more than a discouragingly small percentage of moderately advanced cases; and that the real hope of improving survival rates lies in increasingly early recognition and treatment.

**INTRAEPITHELIAL CARCINOMA.** For many years cancer of the cervix was regarded as an invasive tumor only. Its intraepithelial stage was not recognized until 1933, when Schiller<sup>69</sup> published his historic paper introducing the concept of preinvasive cervical carcinoma—an intraepithelial surface cancer which he thought might be the beginning of the invasive tumor. To most pathologists Schiller's concept of a noninvasive cancer was a paradox. But evidence has gradually accumulated to confirm the malignant nature of the preinvasive lesion, so that now most gynecologists accept Schiller's hypothesis as an established fact<sup>5,19,22,29,49,63</sup>. The adjective "preinvasive" is not strictly accurate, and a more descriptive term such as, "intraepithelial" or "noninvasive cancer," or "carcinoma in situ" is more acceptable.



Sufficient data are now available for an accurate description of the disease: It is a preclinical stage of cancer and its diagnostic findings are histological. Microscopically, the cells have all the characteristics of invasive or metastatic carcinoma, but there is no invasion<sup>\*</sup>; the cellular changes involve the full thickness of the epithelium; and the adjacent areas of cervical epithelium frequently show hyperactivity of the basal cell layer<sup>5,22,29,62,63,69,77</sup>. The cancer usually begins on the cervical portio at or near the mucocutaneous junction; the portio is almost always involved to a greater or lesser degree and the lesion may spread to the adjacent vaginal wall; endocervical involvement is present in more than half of cases and the endocervix may be the only area affected<sup>10,49,63</sup>. The lesion has no characteristic clinical appearance<sup>19,22,63</sup>. Intraepithelial cancers have frequently been found with benign lesions, but are being detected in grossly normal, asymptomatic cervixes more and more frequently because of the widespread use of diagnostic screening methods<sup>20,21</sup>. Although carcinoma in situ is in itself asymptomatic, it has often been found in conjunction with lesions that cause irregular bleeding<sup>19,22</sup>. The average age of women with intraepithelial cancer is about 38 years—approximately 11 years less than that for patients with clinical invasive cancer<sup>22,61,63</sup>. The frequency with which it is being diagnosed is startling. Several investigators have reported an incidence of about 1%<sup>14,20,21,22,61</sup>. If this were confirmed we would have to accept the amazing

fact that one woman in every hundred has a cervical cancer; this seems unlikely.

A number of clinically important problems concerning intraepithelial cancer remain unsolved. The first is the relationship of hyperactivity of the basal cell layer to the development of intraepithelial cancer. The pathologic appearance of the hyperactive cells suggests a premalignant lesion<sup>22</sup>. A smattering of clinical evidence is appearing to suggest that this altered activity may be precancerous, but proof is lacking<sup>22</sup>.

Equally important is the relationship of intraepithelial to invasive cancer. An increasing number of instances are being reported in which invasive cancer has developed at intervals, varying up to 37 years<sup>58</sup>, after an initial biopsy that showed carcinoma in situ<sup>\*†</sup>. Additional evidence that intraepithelial cancer is a stage in the pathogenesis of invasive cancer is the fact that complete study of some cervixes that were found by random biopsy to harbor intraepithelial cancer have shown areas of invasion later<sup>22</sup>. These observations, together with the histologic picture, are sufficient evidence to indicate that noninvasive cancer is a stage in the pathogenesis of at least some invasive cancers. The percentage of untreated noninvasive cancers that will eventually become invasive has yet to be determined and there is no indication as to the percentage of clinically invasive cancers that were once intraepithelial cancers. It is probable that all intraepithelial lesions do not become clinical cancers and that all gross

\* Pathologists differ in their use of the term "invasion"<sup>19,22</sup>. The most reasonable criteria, from a therapeutic point of view, would seem to be penetration of the basement membrane and invasion of the stroma<sup>13,19</sup>. But some include extension into the cervical glands without stromal involvement<sup>22</sup>. Additional disorder is caused by the fact that some investigators fail to exclude from their reports on intraepithelial cancer, cases of microscopically invasive cancers that were originally classified as intraepithelial but were proved to be invasive upon review. This confusion of terms and classification will lead to inaccurate statistics and possibly to improper therapy unless it is corrected.

†Galvin and Te Linde<sup>22</sup> collected 16 cases from reports of 7 investigators, added 1 of their own.

cervical carcinomas are not preceded by detectable intraepithelial malignant alterations.

**DIAGNOSIS.** Since the earliest cervical carcinomas present neither signs nor symptoms, their detection depends entirely upon the application of laboratory methods of diagnosis. It is fortunate that practical techniques for detecting early cervical cancers have been perfected simultaneously with the establishment of criteria for their diagnosis. Although there is only one method by which the diagnosis of any cervical cancer can be confirmed—namely, cervical biopsy (knife cone biopsy with curettage)—there are 2 methods by which its presence may be suspected: random cervical biopsy and cytologic smear. The latter has been enthusiastically studied and developed since it was introduced by Papanicolaou in 1928<sup>52</sup>. The result is a voluminous literature which has established the value of the cytologic smear as a presumptive test but has neglected the difficulties of its practical application.

The technique<sup>21,51,53,55,56</sup> by which a smear specimen is obtained and prepared for examination is simple (a specimen scraped from the portio, supplemented by one aspirated from the endocervix, provides the best sample<sup>3,51</sup>). Its study and interpretation, however, are difficult, time consuming, and require the skill of a specially trained cyto-pathologist<sup>2,21,25,51,53,54</sup>. It can detect an average of probably 90% of cervical cancers—different groups report variations in accuracy of from 70% to 99%—and false negatives are usually less than 5%<sup>3,21,25,28,34,36,38,63,85</sup>. As a screening method, overall accuracy is deceptively good, approaching 100%<sup>25</sup>, because of the overwhelming number of benign and, therefore, correctly diagnosed, lesions composing the group.

The cytologic smear method has two advantages over biopsy: The first is the ease with which the specimen

is obtained. This simplicity encourages its use<sup>66</sup>. The second is that the specimen is composed, at least theoretically, of samples from the complete epithelial surface of the cervix<sup>57,66</sup>. The complete coverage effected by the smear technique accounts for the increasing number of early cancers that are being detected by smear although missed by random biopsy<sup>21,36</sup>. This demonstrated ability and the advantages listed are the bases for the hypothesis that the vaginal smear is the better method for discovery of very early cancers<sup>28</sup>.

At present, the practical use of the vaginal smear method for cancer detection is limited to the study of patients with cervical abnormalities or symptoms suggesting uterine disease; and to the screening of small groups of apparently normal women. The potential usefulness of the smear method as a screening technique is unlimited<sup>20,21,62,67,68</sup>; but the fulfillment of a program for regularly screening all women seems impossible when one considers the size of the task<sup>13,25,60,87</sup>. Since the main difficulty in such an undertaking is the time required for studying the smear specimens—usually estimated as 10 to 15 minutes<sup>34</sup>—the hope of accomplishing it appears to depend on further simplification of the method<sup>2,24,60,87</sup>.

The chief disadvantage of cervical biopsy is its random character. A single biopsy will often miss a minute cancer or will depict a carcinoma as intraepithelial when in an adjacent area it may be invasive. Several modifications have recently been made in the technique of cervical biopsy to adapt the method to the detection and confirmation of early cancer. Multiple biopsies—excising two or more separated segments of cervix have been substituted for the single random or "office" biopsy. The value of each biopsy has been increased by a change in histologic interpretation—cancer

elsewhere in the cervix is suspected from the presence of abnormal basal cell hyperactivity in the biopsy. A random biopsy which shows intra-epithelial cancer may, therefore, suggest hidden invasion; one which shows abnormal basal cell changes may point to a hidden or potential cancer; a negative biopsy may have missed a small carcinoma and its adjacent changes<sup>22</sup>. The deficiencies of random biopsy and the need for a method of confirming tiny cancers detected by the smear technique<sup>4</sup> have led to development of the most accurate method of diagnosing cervical cancer: the knife cone biopsy combined with endocervical curettage. Since this is a supplementary technique which requires study of additional cervical tissue, the random biopsy or smear should be reported before cauterization or electrocoagulation of the cervix is allowed to destroy the cellular morphology of the area under consideration<sup>1</sup>. The endocervix is curetted, following which the cervical portio and mucocutaneous junction are completely excised. Study of this tissue affords unequivocal proof of the presence or absence of cervical cancer. It should be employed not only in cases requiring complete cervical study but as a screening method for all gynecological patients who are operated upon without removal of the cervix. Similar laboratory study is indicated for all cervixes that are removed incidentally at operation, because they may contain unrecognized cancer.

If "suspicious" biopsies are followed by knife cone biopsies, it is probable that the combined study will detect almost all cases of cervical cancer. It is not difficult to take a random biopsy in the office. Combining the two forms of biopsy seems practical, therefore, for both the clinician and pathologist and may be useful as a screening technique<sup>12,30</sup>. Cox *et al.*<sup>12</sup> in a study of 171 cases demonstrated

the effectiveness of the method. They found 7 suspicious cases by random biopsy, of which 3 proved to be intra-epithelial cancers and 2 early invasive carcinomas by the use of knife cone biopsy. A similar routine has been employed at this hospital for some years and, as far as is known, no cancer has been missed: 36 cases were diagnosed as carcinoma in situ by an original biopsy, but complete study<sup>58</sup> showed invasion in 18.

It is apparent that the 2 methods by which early cervical cancer can be detected—smear and biopsy—have identical aims and indications. Although the accuracy and practicality of each method varies, either can detect the great majority of cancers<sup>23</sup>. They are not competitive methods. When both can be employed, the combination increases accuracy and is, therefore, the ideal method of cancer detection<sup>3,21,28</sup>. When only one is available or practical in a given instance, it should be used confidently but with an awareness of its limitations—namely, that it may miss cancer and that, when the vaginal smear method is employed, a positive report must be confirmed by microscopic study of sufficient cervical tissue.

**TREATMENT.** With the improvement in diagnostic techniques, more and more cases of early cervical cancer are being discovered. Some are intra-epithelial carcinomas, for which there is no precedent for treatment. Others are early invasive cancers, most of which would have been treated in the past with Roentgen rays and radium. However, dissatisfaction with the imperfect results of irradiation and the need for a method by which to treat noninvasive cancers have caused some gynecologists to re-explore surgery as a method for treatment of cervical carcinoma.<sup>1</sup>

Because carcinoma in situ is a localized lesion, it is best suited for surgical

excision. Assuming that invasion is absent, total hysterectomy with excision of a small cuff of vaginal epithelium should cure 100% of cases. Although trachelectomy may cure some surface cancers, the malignant nature of the lesion and the undiscernible extent of its spread indicate the need for a more radical type of operation to assure complete excision of the carcinoma<sup>19,63</sup>. Conservation of an ovary is probably permissible if the patient is young<sup>19,22</sup>. To the operative method just described, Te Linde and Galvin<sup>77</sup> have added parametrial excision, because of the frequency with which microscopic malignant invasion is found by study of the cervixes after their removal. This addition increases the hazard of operation because it requires ureteral dissection. Employment of knife cone biopsy will permit proof of the presence or absence of invasion before final treatment<sup>12,19,21,46</sup>. If invasion is absent, the more radical procedure is unnecessary; if it is present, although only microscopically, disregard of lymph node metastasis would seem unwise. Excision of lymph nodes is an essential part of the surgical attack on invasive cervical cancer.

Two types of operations for invasive cancer are being investigated in the present surgical revival: the so-called Wertheim operation<sup>10</sup> and the regional lymphadenectomy of Taussig<sup>75</sup>. The former includes a group of operations in which total hysterectomy and bilateral salpingo-oophorectomy are combined with the removal of various amounts of the vagina, parametria, cul-de-sac, and regional lymph nodes<sup>8,11</sup>. Regional lymphadenectomy, when employed as the only surgery, is always combined with irradiation therapy and is designed to remove the pelvic nodes to which cervical cancer metastasizes: the ureteral, iliac, obturator, and hypogastric groups<sup>74</sup>.

The surgical experiment has been in

progress for so short a time that complete results will not be available for some years. However, we can reach certain tentative conclusions and we can define the problems that any re-examination of surgery must answer.

To date, the important conclusion is that radical surgery can now be performed safely in carefully selected cases by skillful gynecological surgeons trained in the technique of the operation. Meigs<sup>42</sup>, who employs surgery in 10% to 15% of cases, has reported 91 Wertheim type operations without a surgical death. Although this record has not been duplicated, it is probable that the operation can be performed in selected early cases, comprising possibly  $\frac{1}{4}$  of all cervical cancers, with an operative mortality of no more than 5%<sup>8,17,64</sup>. Brunschwig<sup>9</sup> is demonstrating that extremely radical surgery—complete excision of the pelvic viscera—can be done with a low surgical mortality rate in advanced cases with the help of good modern pre-operative and post-operative care. Meanwhile, Taussig<sup>75</sup> and Morton<sup>44</sup> have demonstrated the safety of regional lymphadenectomy, and Nathanson and Parsons<sup>57</sup> have developed an extraperitoneal approach for removal of regional nodes which is equally complete and may prove to be safer than the transperitoneal approach. The most frequent serious complication of radical pelvic surgery—ureteral fistula—has been almost eliminated by preservation of the ureteral blood supply<sup>12,43</sup>. Because the mortality rate of irradiation is admittedly lower than that of surgery<sup>23,73</sup>, results showing the safety of surgery are an encouragement for the continuation of the experiment rather than an argument in favor of surgical treatment.

One undeniable indication for excising a cervical cancer is the presence of a radioresistant tumor. The frequency of this tumor type is uncertain; it has

been described as uncommon<sup>11,71</sup> and has been estimated as high as 50%<sup>26,27</sup>. It can be recognized clinically by observing the response of the neoplasm to irradiation, but this is unsatisfactory, because by the time an unfavorable response is confirmed, the lesion may be inoperable or the patient may have become a poor surgical risk. Several investigators suggest that radioresistance can be detected preclinically by study of vaginal smears or biopsies taken during irradiation therapy<sup>26,27,32</sup>. If this is confirmed a method will be available for scientific segregation of a group of cervical cancers which cannot be cured by irradiation and for which radical surgery is the only recourse.

Radioresistance of metastatic cancer in lymph nodes is frequently proposed as an indication for Wertheim type operation or regional lymphadenectomy following irradiation<sup>11,26,64,71,74,75</sup>. The degree to which these lesions are radioresistant is uncertain. Past clinical experience suggested that irradiation rarely if ever destroyed cancer in nodes<sup>8,40,46,64,74</sup>, but more recent evidence indicates that it does, at least, in some cases<sup>45,64</sup>. If modern irradiation can destroy cancer in lymph nodes as frequently as surgery, one of the main and historic arguments for the surgical treatment of cervical cancer is defeated<sup>64</sup>. It will be important, therefore, to determine how frequently modern irradiation can destroy metastatic cancer, since surgery can eradicate proved lymph node metastasis in only 20% of patients<sup>8,64,74,75</sup>. The present re-examination of surgery should answer this question and should determine whether lymph node metastasis is or is not an indication for the operative removal of the nodes. Meanwhile, the determination of the radioresistance of tumors is of practical value in determining which patients may be benefited by regional lymphadenectomy: salvage cannot be in-

creased by lymph node excision if the primary tumor is both radioresistant and inoperable<sup>26</sup>.

The argument is sometimes put forward that curative surgery results in lower morbidity and fewer complications in early cancer than curative irradiation. However, the question is not one that lends itself to statistical analysis<sup>14</sup>. Clinicians who have had to treat a significant number of severe post-irradiation reactions may favor surgery. Those who have been plagued by surgical patients complaining of severe bowel, bladder, and ureteral injuries or a functionless, short vagina may favor irradiation. It has been proved that good results with few complications can be obtained by good surgery performed upon carefully chosen patients<sup>42</sup>. But this is also true of irradiation therapy, particularly in a similarly selected group treated carefully by a competent therapist<sup>35</sup>. Many of the complications of irradiation therapy are due to overtreatment resulting from the combined use of radium and Roentgen rays<sup>46,71</sup>. There is recent evidence that early cases do not require Roentgen-ray treatment in conjunction with radium, and the elimination of Roentgen rays from the therapy of these early cases may reduce the number of complications<sup>78</sup>. The frequency and severity of therapeutic complications that follow various techniques of treatment with similar salvage rates depends more upon the judgment, experience, and ability of the therapist than upon the method of treatment which he uses.

Since inadequate irradiation therapy is followed by poor results, pre-existing complications which might prevent complete treatment may be important indications for surgery. Among these are certain cases of pelvic inflammatory disease, endometriosis with hematomata, vaginal stenosis, pelvic tumors, pregnancy, emotional disturbances, and

lack of cooperation on the part of the patient<sup>11,64</sup>.

It has been suggested that "cure" of cervical cancer by surgery is more permanent than that by Roentgen rays<sup>6,41,64,74</sup>. Garcia and Melville<sup>23</sup> concluded from a study of cases in the literature, that this hypothesis is unproved. The premise that excision of the malignant cervix will improve survival rates by preventing local recurrences and the development of new cervical cancers seems equally questionable<sup>11,35,72</sup>.

The major part of this discussion of therapy has been allotted to the surgical method because the revival of surgical excision is still new and experimental and, therefore, of particular interest. Surgery may be expected to play an increasingly important role, particularly in the recently expanding field of early cancer. Irradiation, however, maintains undisputed supremacy as the treatment of choice for most cases of cervical cancer. New developments, and the lessons learned from experience, are making irradiation safer and more cancerocidal. Probably the most important advance in irradiation therapy has been establishment and application of the concept of tissue tumor dosage<sup>23,37,47,48,50,79,83,86</sup>. By calculating the irradiation which each tumor, its metastases, and the surrounding normal tissue receives, the therapist can assure the greatest, safe dose of irradiation to each cancer. This feature is but a part of an important trend to individualize irradiation treatment rather than to apply it as an inflexible and preconceived pattern to every patient. It also includes variations in therapy required by incidental complications such as debility, sepsis, and anemia<sup>7,11,32,35,59</sup>. Completion of a curative course of irradiation may be possible only after these modifying factors have been corrected. Results are further improved by a more precise

application of therapeutic technique<sup>11,15,16,23,31,32,35,84</sup>, for instance, roentgenologic determination of radium placement<sup>33,37,81</sup>; the development of new therapeutic methods<sup>35,37,65,76,80,82</sup>; and the prompt recognition and treatment of therapeutic complications<sup>23,31,71</sup>.

**Results.** The best method of determining the value of treatment methods is the analysis of their salvage rates. Final evaluation of the modern surgical experiment must await a longer period of observation. Predictions based upon past surgical experience are uncertain and might cause undeserved prejudices. Past surgical results have not equalled those of irradiation; surgery has effected a 5 year "cure" in less than 70% of early invasive cases. Surgical success will always be limited by distant nodal metastasis—not uncommon even in early cases—and by the inevitable incompleteness of the lymph node excision<sup>49,64,71</sup>. Preliminary observations of the recent surgical experiment suggest, however, that safe radical surgery may attain a cure rate comparable to that of irradiation and, in certain instances, will cure patients who would otherwise die. Experience with the combined use of lymphadenectomy and irradiation suggests that it, too, may improve the chances of survival in some cases<sup>26,35,44,45,64,74,75</sup>. The best cure rate which has been proved has been obtained by irradiation therapy. The absolute 5 year salvage of all cases treated by irradiation averaged 35% in a recent collective review; that of Stage I cases was 73% and a number of investigators reported a survival rate of more than 80%<sup>14,23,39,70</sup>.

**Comment.** In conclusion it may be said that irradiation therapy remains the treatment of choice for most patients with cervical cancer; that results of irradiation may be favorably influenced by the addition of regional lymphadenectomy; that radical surgery

can be done safely and has an increasingly important place in treatment of early cancers, particularly of the non-invasive type, and possibly in selected groups of invasive cancer; and that

individualized therapy, is the best method of curing the greatest number of patients and, at the same time, assuring their comfort and happiness.

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# PEDIATRICS

UNDER THE CHARGE OF

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## THE PHOSPHATASES IN RELATION TO CLINICAL PEDIATRICS

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THE PHOSPHATASES partake in the dynamic equilibria of the body economy by breaking down enzymatically the organic esters of phosphoric acid. They enter actively into the intracellular hydrolysis of organic phosphates of all sorts, including the phospholipids, phosphoproteins, nucleotides, and phosphorylated carbohydrates. They appear to be omnipresent in nearly every tissue of the body. They are also demonstrable in the circulating blood, in concentrations which may become increased or decreased in certain disease states. Studies of their concentration in the circulation have proved of practical diagnostic significance, even though the causative mechanism of these changes is far from adequately elucidated.

The phosphatases are usually separable into 3 main groups: phosphomonoesterases, phosphodiesterases and pyrophosphatases. Separation of one from another is based fundamentally upon the molecular architecture of the phosphatic substrates used in the testing for these enzymes. Some appear to be highly specific, such as choline phosphatase, ribonuclease, thymonucleodepolymerase, and 5-nucleotidase. The phosphomonoesterases are the variety

ordinarily found in the blood stream, and will receive chief attention in this Review. In the ensuing text the term phosphatase is used as an abbreviation for phosphomonoesterase, unless otherwise stated. The symbol AP is used for "alkaline phosphatase," and SAP for "serum alkaline phosphatase."

TYPES OF PHOSPHATASE. Folley and Kay<sup>32</sup> have described 3 types of phosphomonoesterases which may be found within human tissues. There are the alkaline phosphatases with a range of activity from about pH 6.0 to 10.0 and a pH optimum between 9.0 to 10.0. These occur in bones, kidneys, liver, intestines, mammary glands, lungs, blood plasma, and miscellaneous other sites. A second type is the acid phosphatases, with a pH optimum of 4.5 to 5.0, found to some extent in the spleen, liver, pancreas and kidney, and to an unusual degree within the prostate. A third phosphatase, also called an acid phosphatase, has been demonstrated in the erythrocytes. This has a pH optimum of approximately 5.3, and appears to differ in certain properties from the other acid phosphatases.

Many attempts have been made to differentiate these enzymes in the various tissues from each other, but

without much success. It is probable that the phosphomonoesterases are not highly specific and that they will attack a large variety of organic monophosphates.

Most of the phosphatases are highly sensitive to changes in hydrogen ion concentration and can be activated by magnesium salts. Many activators and inhibitors have been uncovered by the biochemists, but this aspect of their chemistry is beyond the scope of this discussion. In clinical testing all the variables are standardized with the exception of the content of enzyme free in the blood plasma. Good reviews on the chemistry of the phosphatases and their substrates can be found in the reports by Folley and Kay<sup>32</sup>, Moog<sup>69</sup>.

**CHEMICAL STRUCTURE.** The actual chemical structures of the different phosphatases are not known. They all appear to have a complex proteinous structure, with molecular weights ranging from 6,000 to 10,000. Considerable work has been done which shows apparently significant differences in the alkaline phosphatases from different sources but thoroughly purified preparations will be needed before the uncertainties regarding the nature and chemical identity of the phosphatases can be resolved.

**PHYSIOLOGICAL SIGNIFICANCE.** The roles played by the phosphatases within the body economy seem to depend largely on where they are situated within the body. The functions which have attracted widest interest are those concerned with absorption of food from the gastrointestinal tract, dephosphorylation within the liver, reabsorption of glucose by the kidney tubules, and deposition of lime salts within the bones.

**GASTRO-INTESTINAL TRACT.** In gastrointestinal absorption, the glycerol from the fats is first linked with a phosphate ion through the mediation of a

phosphorylase to form glycerophosphoric acid which is then hydrolyzed by AP and the glycerol absorbed. AP also takes part in the synthesis of lecithin from phosphotidic acid and choline and in the formation of a diglyceride from lecithin. Prolonged fat feeding results in an increased SAP which presumably is of intestinal origin. AP is also concerned with nucleoprotein metabolism and catalyzes the hydrolysis of mononucleotides to nucleosides and phosphate. The nucleosides may then be absorbed directly or be hydrolyzed to purines and carbohydrates with the aid of purine nucleosidase and then absorbed. AP also liberates phosphoric acid from phosphoserine and from peptones containing this ester.

In gastro-intestinal carbohydrate absorption, both glucose and galactose, and fructose to a lesser extent, are converted to phosphoric esters in the mucosa by phosphorylase. These esters are subsequently hydrolyzed by AP and the liberated monosaccharides enter the portal blood stream. Alimentary hyperglycemia results in increased SAP.

**KIDNEY.** Within the kidney tubules the glucose which dialyzes through the glomeruli is first phosphorylated in the course of tubular reabsorption by the kidney phosphorylase<sup>29</sup>. AP hydrolyzes this ester so that the glucose can be returned to the blood stream. Wilmer<sup>69</sup> believes that there is a direct correlation between the functional activity of the renal tubule and its AP activity.

**BONE.** AP occurs abundantly in embryonic bone and ossifying cartilage and in osteoid tissue which ultimately will become bone, but not in cartilage of the non-ossifying type. It is also present in teeth. The enzyme is usually though not invariably associated with the tissues in which hard structures are being abnormally formed<sup>69</sup>.

The explanation for calcification is much more complicated than being simply a chemical precipitation of calcium and phosphorus as a consequence of the presence of AP in some quantity in certain tissues<sup>32,69</sup>. AP is present in organs which do not normally calcify, such as intestinal mucosa, liver, mammary glands and kidney. Furthermore, in rickets, calcification is arrested although AP is present in abundance in the osteoid tissue near the zone of provisional calcification.

Bone and tooth formation are believed to require a "second" or "inorganic" mechanism. It has been postulated that AP acts on the different gluco phosphoric esters to produce carbohydrate breakdown products and phosphate ions. The phosphate ions then combine with calcium ions until the solubility product of calcium phosphate is exceeded and calcium phosphate is precipitated into the matrix of the bone<sup>12</sup>.

**EXCRETION.** AP is excreted in the feces and to some extent in the urine. Burgen<sup>22</sup> measured urinary AP and found it to be scanty and irregular with no variation with age and sex. Lawrie<sup>61</sup> has found that a normal adult excretes an average of 23.0 units of alkaline phosphatase (Bodansky method) per gm. dry weight of feces. This presumably is derived from the waste AP from the bile, succus entericus, and others.

#### ALKALINE PHOSPHATASE IN TISSUES.

**Methods:** Determination of AP in tissues can be done either by chemical extraction or histologic staining. Most tissues contain both acid and alkaline phosphatase. Extractions are performed by grinding and macerating a known quantity of the tissue and then autolyzing the mixture for a variable period of time in water or chloroform-water. The mixture is then filtered and the enzyme activity of the

filtrate is determined by one of the methods used in the measurement of SAP. Drabkin<sup>29</sup> has found that homogenization of the powdered tissues will yield much higher activity values.

The enzyme was demonstrated histologically simultaneously in 1939 by Gomori<sup>39</sup> and Takamatsu<sup>86</sup>. One imbeds the tissue in paraffin, cuts and mounts the section on a glass slide and then allows the AP of the particular tissue to act on a substrate of sodium glycerophosphate and calcium nitrate. The glycerophosphate is hydrolyzed and the liberated phosphate ion joins the calcium ion until the solubility product is exceeded and the calcium phosphate is precipitated *in situ*. The calcium phosphate is then changed to a visible form either by reacting with added silver nitrate to form brown to black silver phosphate or by reacting with cobaltous nitrate to form cobalt phosphate which is subsequently converted to black cobalt sulfide by the addition of ammonium sulfide. The tissue may then be counterstained. Menten *et al.*<sup>68</sup> have described a histochemical azo dye test for kidney AP which is said to give results comparable to those of Gomori and Takamatsu. Other modifications have been likewise proposed.

Many variables are inherent in both the tissue extraction and the tissue visibility methods. Aside from maintaining precise control of pH and temperature, one must deal with many inherent difficulties such as magnesium ion content, and others. Williams<sup>98</sup> has stated that phosphatase may be activated as much as 5,000% by the proper concentration of magnesium ions.

Few successful attempts have been made to correlate SAP and tissue AP quantitatively, though it is well known that in diseases of either bone or liver both the SAP and tissue AP may become elevated.

**Bone.** AP is found in nearly all grow-

ing and ossifying bone. In stained preparations it is most abundant in the osteoblasts and proliferating cartilage cells of the epiphyseal portions of the bone and in the cells of the inner layer of periosteum in the metaphysis. Most of the studies on bone have been chemical in nature, for it was not until comparatively recently that Barger<sup>5</sup> and Lorch<sup>62</sup> perfected the technic for the histochemical demonstration of the enzyme in bone.

Woodard<sup>101</sup> has demonstrated that the average AP content of the cortex of adult bone is between 0.04 and 0.15 units per gm. (Bodansky method) while that of children's bones is between 0.16 and 3.3 units per gm. Acid phosphatase activity in normal bone was barely detectable. Regenerating bone may have up to 50 times the AP content of normal bone. Bakwin and Bodansky<sup>3</sup> found the AP increased in the bone in rickets, fragilitas ossium, osteitis fibrosa, osteomalacia, osteitis deformans and hyperthyroidism.

*Digestive System.* Berliner<sup>10</sup> has shown the tooth buds of the fullterm fetus to be strongly positive for AP. There was no appreciable enzyme activity in adult teeth. Provissimato<sup>72</sup> had stated that the AP of adult teeth increased in dental caries and pyorrhea but this was not verified by Berliner. AP has been found in saliva and in the salivary gland. The problem of the origin of the salivary AP is not wholly solved. Smith<sup>82</sup> stated that it probably came from the desquamated gingival epithelium. However, both Zander<sup>104</sup> and Glock<sup>38</sup> after extensive studies decided that it was probably of bacterial origin, inasmuch as AP has been found in some bacteria. Bray<sup>20</sup> has suggested taxonomic classification of the Corynebacteria on the basis of the AP reaction.

The superficial and occasionally the deep cells of the filiform papillae of the tongue give a positive AP reaction.

The epithelial cells of the gastric mucosa are uniformly negative for AP. AP has been demonstrated in all portions of the mucosa of the small intestine. Koster<sup>59</sup> found a decrease in the intestinal excretion of AP in non-tropical sprue and Heymann<sup>47</sup> noted decreased excretion of the enzyme in rickets, spasmophilia and intestinal infantilism. Kosmann<sup>58</sup> found the AP of the small intestine increased after a fat or protein meal and somewhat after a carbohydrate meal. He estimated that the AP was highest in the duodenum and lowest in the ileum. The large intestine has been universally negative for AP except for some positive capillaries. Kabat and Furth<sup>52</sup> found no AP activity in the human pancreas, but the islets of Langerhans are rich in acid phosphatase<sup>70</sup>.

*Liver.* The distribution of AP in the human liver was studied thoroughly by Wachstein and Zak<sup>96</sup>, who found that normally the cytoplasm of the hepatic cells reacted with only a faint and uneven AP stain. The nuclei, including the chromatin, nucleoli and nuclear membrane, were markedly positive. There was a varying degree of AP in the sinusoidal walls and the Kupffer cells and also in the nuclei of the bile duct epithelium. The endothelium of the larger veins, small arteries and arterioles showed great AP activity while the staining of the bile capillaries was variable. The liver seems to have a higher content of AP than of acid phosphatase, whereas in kidney and blood plasma the reverse is true<sup>29</sup>. The findings with respect to the liver are different in different animal species.

Many studies have been done on the alterations of hepatic AP in the liver diseases. Gad<sup>35</sup> found that AP increased in the dogs liver after ligation of the common bile duct. Wachstein and Zak<sup>96</sup> substantiated this and found the enzyme activity prominent chiefly in the bile capillaries. The AP became

progressively increased with the duration of the obstruction. Wachstein<sup>95</sup> found that the AP in human obstructive jaundice increased markedly in the bile capillaries with little or no increase in the hepatic cell cytoplasm. He noted that the sprouts of biliary proliferation showed no particular enzyme activity. Sherlock and Walshe<sup>80</sup> found an increase of AP in obstructive jaundice throughout all parts of the liver except in the connective tissue.

In liver necrosis Wachstein<sup>95</sup> found no appreciable increase of AP in the degenerating liver cells. The bile capillaries were devoid of the enzyme whereas the proliferating fibroblasts and lymphocytes showed a markedly positive reaction. In hepatic cirrhosis the AP was normal in the undamaged cells and showed no increase in the necrotic cells. There was a variable increase in AP in the bile capillaries and in the connective tissues. Sherlock and Walshe<sup>80</sup> found a variable AP increase in the hepatic cells, and bile canaliculi in hepatic cirrhosis and a definite increase of the enzyme in the sinusoidal and connective tissue. There was a general decrease in the AP in fatty livers. In acute hepatitis Sherlock and Walshe<sup>80</sup> found an increased AP in the hepatic cells, sinusoidal walls and portal tract. Thannhauser<sup>90</sup> found decreased AP in the liver in Von Gierke's disease.

*Urogenital System.* The AP in the kidney is located chiefly in the upper part of the proximal convoluted tubules and to a lesser extent in the lower portions. No AP is seen in the distal convoluted tubules, the loops of Henle, the collecting tubules or in the glomeruli (except in the cat). The smaller renal vessels are usually positive. AP has also been found deep in the transitional epithelium of the urinary bladder. In experimental hydronephrosis of animals the renal AP often shows appreciable diminution<sup>99</sup>. There is a

high content of acid phosphatase in the prostatic epithelium.

AP has been demonstrated in the endometrium and to some extent in the circular muscle layer of the myometrium. Dempsey and Wislocki<sup>28</sup> state that the placenta of the sow, cat, guinea pig and human all contain phosphatases which will split fructose diphosphate, glycerophosphate, lecithin and yeast nucleic acid.

Gomori<sup>40</sup> demonstrated the presence of AP in the lining of the seminiferous tubules and in the epididymis. Macleod and Summerson<sup>63</sup> state that AP is present in the sperm. Furth and Kabat<sup>52</sup> showed it to be present in the spermatogenic cells and basement membrane of the testes. Hexosediphosphatase is present in the nuclei of the human vas deferens<sup>105</sup>.

*Blood and Vascular System.* There is considerable variability of AP content, depending on the organ and species but in general one usually finds a rich deposit in the capillaries, arterioles and venules. Zorzoli and Stowell<sup>103</sup> have found hexosediphosphatase in the intima of the human aorta.

AP activity in the blood and bone marrow cells have been studied by Wachstein<sup>95</sup>. Normally the erythrocytes, lymphocytes, monocytes, eosinophils show no AP, whereas the neutrophils show variable AP. Similarly, in the bone marrow, AP was seen only in the neutrophils of the myeloid series and occasionally in the nucleated red cells, erythroblasts. The principal phosphatase in the erythrocytes was shown by Behrendt<sup>9</sup> to be one with maximal activity at pH of 4.8 to 6.1 (see later discussion).

In the pyogenic infections neutrophils have an increased AP content, particularly in the cytoplasm<sup>95,31</sup>. Patients with infectious mononucleosis or eosinophilia had no increase of AP in these cells.

*Spleen.* Davis<sup>27</sup> first found AP in the

splenic extracts. Bourne<sup>18</sup> found the contents to be in the Malphigian corpuscles and lymphocytes. Kabat and Furth<sup>52</sup>, Gomori<sup>40</sup> and Greenstein *et al.*<sup>42</sup> found AP only in the endothelial elements.

*Lymph Nodes.* According to Kabat and Furth<sup>52</sup> only the endothelial cells of the blood vessel walls are positive for AP. Gomori<sup>40</sup> lists the lymph nodes as having a variable AP content.

*Nervous System.* The AP content of the brain seems to be based on the degree of vascularity, inasmuch as AP is stainable only in the endothelium of the blood vessels in the central nervous system<sup>60</sup>.

*Respiratory System.* Kabat and Furth<sup>52</sup> and Gomori<sup>40</sup> found a positive reaction in the brush borders and the submucosal glands of the trachea and bronchi. There was an occasionally questionable AP reaction in the alveolar septa of the lung and a more or less uniformly positive reaction in the pulmonary capillaries.

*Endocrine System.* AP has been found in the adrenal cortex but not in the medulla<sup>40</sup>, and especially in the zona reticularis<sup>52</sup>. The capillaries are also positive. In the thyroid, AP is found only in the capillaries<sup>40,52</sup>. Gomori<sup>40</sup> was unable to demonstrate AP in the parathyroid. In the pituitary, AP is seen in the neurogenic cells of the posterior lobe, the capsule and the capillaries but not in the anterior lobe<sup>52</sup>.

*Miscellaneous.* Muscle is uniformly negative except for the capillaries. The content of AP in the skin is variable. Wilmer<sup>39</sup> was unable to demonstrate the enzyme in the inclusion bodies of vaccinia, herpes simplex, fowl pox or tracheolaryngitis.

*Neoplasms.* Research into the AP content of neoplastic tissue is comparatively new. Landow and associates<sup>60</sup> studied AP in central nervous system neoplasms and found it in the

meningiomas but absent in the astrocytomas, oligodendromas and glioblastomas. Woodard and Higinbotham<sup>100</sup> found the AP content of osteogenic sarcomas highly variable with no correlation with the histologic structure. Benign osteochondromas and giant cell tumors showed no enzyme activity, while malignant giant cell tumors tended to be positive. Embryonal adenomas of the testes<sup>100</sup> and also thymomas<sup>42</sup> contained AP, whereas malignant epitheliomas, carcinomas of the breast, liposarcoma, malignant melanoma, adamantinoma and hypernephroma did not<sup>52</sup>. Fibroadenomas of the breast showed some AP in the ducts. Carcinomas of the intestine were questionably positive<sup>52</sup>. Wilm's tumor has exhibited a moderate amount of AP particularly in the stroma<sup>52</sup>. The cells of acute myeloblastic leukemia had no increase in AP and perhaps actually showed some decrease compared to those of the normal person<sup>55</sup>. Those of chronic leukemia were consistently negative<sup>55</sup>. Kabat and Furth<sup>52</sup> could find no AP in the cells of acute lymphatic leukemia. A range of AP activity from 0 to 115 units per gm. (Bodansky method) has been found in extracts of osteogenic sarcoma tissue by Woodard<sup>101</sup>. No correlation was found between phosphatase activity and histologic structure of the tumors. Soft-part metastases from osteogenic sarcoma had AP activities of the same order of magnitude as the primary tumor. The phosphatase of extracts of giant cell tumors and of endothelioma of bone were active mainly in acid solution.

**ACID PHOSPHATASE IN ERYTHROCYTES.** The acid phosphatase in human erythrocytes is distinctly different from the acid phosphatase which occurs in the blood plasma normally or the (probably) other variety which appears in the plasma of patients with metastasizing cancer of the prostate

Studies by Sullivan, Gutman and Gutman<sup>85</sup>, Behrendt<sup>9</sup>, and King, Wood and Delory<sup>56</sup>, have confirmed the individuality of this phosphatase. It has a strong activity in the range between pH 4.8 and pH 6.1, with an optimum at about pH 5.3. Curiously, its action upon B-glycerophosphate is slow compared to a much stronger activity against the phenol phosphates. It displays little activity against the phosphoric esters of alcohols, glycerol and hexoses. With phenolphosphate as substrate, King and Armstrong found the values in normal persons to be from 200 to 400 units per 100 cc. with an average of 340 units<sup>55</sup>. They failed to discover any abnormality in disease states. These figures were secured by determinations made from blood cells laked with distilled water. The cells were washed and subsequently hemolyzed.

Behrendt has recently reported studies made on whole blood, blood plasma, hemolyzed erythrocytes and suspensions of erythrocytes in saline solutions<sup>9</sup>. When the phosphatase activity of hemolyzed cells was compared with plasma phosphatase from the same blood sample it was noted that the phosphatase activity of the red cells of pH 8.9 in terms of units was more than twice as great as that of the plasma, whereas at pH 4.9 the red cells possessed an activity at least a hundredfold that of plasma. Behrendt's averages for the acid red cell phosphatase was between 94.4 and 305.3 Bodansky units, with an average of 159.1 units. These values were somewhat lower than those of King and Armstrong. Experiments with whole blood revealed that the hydrolytic effect upon buffered phenolphosphate was almost as strong as that of laked erythrocytes when the blood was prevented from being hemolyzed during the testing period. The acid phosphatase activity of the red cells proved

to be lower when they were suspended in plasma than when suspended in saline solution. Inasmuch as washings of these red cells were free of enzymatic activity, it was evident that at pH 4.9, phenolphosphate must penetrate through the red cell membrane in order to be acted upon by the contained phosphatase. Rustbrunner<sup>77</sup> states that the acid phosphatase of the erythrocytes when measured at pH 6.8-7.0 fluctuates with age. There is an increased phosphatase in the erythrocytes of the newborn which subsequently decreases and then later increases in old age.

**SERUM PHOSPHATASE LEVELS.** Tests for the content of the phosphatases in the circulating blood have been performed in almost every kind of illness and hundreds of studies recorded. Most of the methods of blood analysis determine and express the content of AP in terms of measurements per unit volume of serum, despite the fact that within the body the circulating enzyme is in plasma rather than serum.

The presence of the phosphatases within the circulation is believed to result from overflow from the organs where the enzyme occurs in large amounts, chiefly liver, kidneys and bone, rather than indicating physiologic functional activity upon the constituents of the blood itself. The phosphatase contained within the red cells may be an exception. According to this interpretation, an elevated plasma content of either alkaline or acid phosphatase represents either a lack of balance between leakage into the circulation and excretion by the kidney and liver, or else a continuously greater current of the enzyme from site of origin to site of excretion. Much still remains to be learned about the metabolic cycle of the phosphatases.

Because the phosphomonoesterases

are not highly specific for single substrates, it is possible to utilize any one of a number of simple phosphatases as substrates for clinical testing. The Bodansky method measures, under standardized conditions, the liberation of inorganic phosphates from B-glycero-phosphate<sup>10</sup>. One Bodansky unit is defined as that amount of enzyme in 100 cc. of plasma which will liberate 1 mg. of phosphorus (as the phosphate ion) during the first hour of incubation under the conditions described. With the Kay or Jenner-Kay method, one unit represents the liberation of 1 mg. of phosphorus as free phosphate from an excess of disodium B-glycero-phosphate at pH 8.8 in 3 hours when kept at a temperature of 37.5 C.<sup>53,54</sup>. The King-Armstrong method utilizes disodium phenylphosphate as substrate and measures the phenol in 30 minutes under the conditions of the test. Several later simplifications of the King-Armstrong technic have found acceptance in many laboratories. It is estimated that one Jenner-Kay unit equals approximately 2 Bodansky units. One King-Armstrong unit is approximately equivalent to one Jenner-Kay unit. Huggins and Talalay<sup>49</sup> have proposed sodium phenolphthalein phosphate as buffer with colorimetric readings of liberated phenolphthalein as the index of enzyme activity. To escape from the need for venipuncture demanded by the above methods, Bessey, Lowry and Brock<sup>11</sup> have developed a micromethod which can be done on fingertip blood. This employs paranitrophenyl phosphate as the substrate, and the results are expressed in nitrophenol units. One nitrophenol unit is approximately equivalent to 1.79 Bodansky units.

The technics of testing for the acid phosphatases are much the same as for the alkaline variety except that different buffers are employed in order to obtain the desired acid pH of the environment.

Because of the diversity of methods in clinical practice, it is especially important to know which procedure is being employed by the laboratory whose services are being utilized, and what the limits of normality are, not only for that particular procedure but for that individual laboratory as well.

**SERUM ACID PHOSPHATASE.** A small amount of acid phosphatase can ordinarily be demonstrated in the serum of every person, regardless of age or sex. An elevation in serum acid phosphatase is almost never seen except in carcinoma of the prostate which has broken through its capsule to invade the periprostatic tissue or metastasize distantly to bone. The source of the increased serum acid phosphatase in such malignancies is clearly the prostatic epithelium itself or the cancerous epithelioma derived from it. McWhirter<sup>67</sup> has described slight elevation in serum acid phosphatase in ankylosing spondylitis of males.

The production of acid phosphatase by the prostate is influenced to a large extent by gonadal activity. It does not appear in any quantity until adolescence is attained, and the amount produced can be increased by giving of androgens or decreased by giving estrogens.

Large quantities of acid phosphatase are present in adult semen. The origin of this enzyme seems to largely lie in the prostate. Prostatic fluid obtained by massage is rich in this enzyme, whereas the other secretions which combine to make up the ejaculate do not contain any and in aspermia the ejaculates have phosphatase values as high as ejaculates containing spermatozoa. No other body fluid contains acid phosphatase in anywhere near the concentration reached in the seminal fluid (apart from the blood in carcinoma of the prostate). Riisfeldt<sup>75</sup> has applied this knowledge to the medico-legal problem



of proving or disproving the presence of semen in dried spots on clothing. The recovery of large amounts of acid phosphatase, from such spots, is presumptive identifying evidence when an accusation of rape has been made.

**SERUM ALKALINE PHOSPHATASE.** Generally speaking, the SAP level is elevated in osteogenic sarcoma, rickets, osteomalacia, generalized osteitis fibrosa cystica, osteitis deformans (Paget's disease), pregnancy (especially the last months), secondary carcinoma of bone, infectious mononucleosis, idiopathic steatorrhea, and jaundice<sup>81</sup>. A SAP increase, therefore, cannot be interpreted as being diagnostic or even indicative of any one disturbance, in the absence of other pertinent information regarding the patient.

**ALKALINE PHOSPHATASE.** The origin and excretion of the circulating SAP is far from settled. Armstrong and Banting<sup>2</sup> suggested that the osseous system is the origin of SAP and the liver the excretory organ. This theory is based in part on experiments which showed that the removal of the abdominal viscera either singly or in combination did not substantially lower the level. Bodansky<sup>10</sup>, on the other hand, has shown that alimentary hyperglycemia results in an increased SAP and that induced liver disease without obstruction has the same result. He postulates that the rise in SAP is of osseous origin in bone diseases and of hepatic origin in liver diseases. This is supported by Gould<sup>41</sup>, who found that prolonged fat feeding increased the SAP. The level of SAP tends to remain at a more or less constant level from day to day, being unaffected by meals and incidental occurrences<sup>94</sup>.

In animals, ligation of the common bile duct results in an increase of both SAP and intrahepatic AP without an increase of AP in any of the other viscera. Similar findings have been

noted in obstructive jaundice in humans, with prominent accumulation of AP in the region of the bile capillaries. Three theories have been postulated to explain the increase of AP and SAP: (1) The enzyme accumulates because of decreased excretion in the bile. (2) The AP already present exhibits greater activity as the result of formation of an "activator substance" or a decrease in some "inhibitor substance." (3) There is an unusual formation of AP within the liver cells<sup>35</sup>.

Reference may also be made to the observations that sera with high AP content from patients with obstructive jaundice and Paget's disease, as well as from dogs with experimental bile duct obstruction, are capable of augmenting the AP activity of normal serum when these are incubated together for 24 hours<sup>24,33</sup>. Similarly, when plasma from such dogs is injected into normal dogs, the elevation in SAP titer which ensues is higher than can be accounted for by adding the phosphatase activity of the injected plasma. In the dog experiments Cantarow and Miller<sup>25</sup> found very little of the infused phosphatase to be excreted in the bile. This suggested that a normally functioning liver does not actively remove phosphatase of this type from the blood and therefore contradicts the hypothesis that it originates in extrahepatic tissues.

**NORMAL VALUES FOR SAP IN CHILDHOOD.** Talbot and associates have published the figures on SAP for 70 healthy children between 2 and 10 years of age<sup>88,89</sup>. The values ranged from 4.5 to 12 units by the Bodansky method. The average for the entire group was 7.2 units, and there was no apparent variation in relation to changes in age or between boys and girls. These values are essentially the same as those found by most workers, including Bodansky himself, and by common agreement are accepted by

most institutions as "normal." In infants under 1 month of age the plasma AP tends to be a little lower than in older infants and children<sup>7,84</sup>.

Bodansky and Jaffe<sup>17</sup> were among the first to survey the levels of SAP in normal children and adults as well as in some of the diseases of the bones, using the Bodansky method. The average for 27 children was found to be 7.3 units per 100 cc., with values ranging from 3.1 to 13.1. Values from 10 to 13 units were common between the ages of 10 and 15 years. In about 300 other children between 1 and 15 years of age hospitalized for a variety of clinical conditions (excluding anemia, malnutrition, jaundice, and known diseases of bone) the range was approximately the same, from 5 to 14 units, with an average of about 7.5 units. A few of the infants in the first few months of life had values of 15 to 20 units. In contrast the average for adults was 3 units with a range from 2 to 4 units. There was relatively little variation in the values between 2 and 10 years of age. In a 16 year old boy with osteosclerosis fragilis generalisata (Albers-Schonberg disease) the SAP fluctuated from 15 to 21.5 units. High values were found in association with jaundice whereas anemia gave low values. The observations on the children, and on adults with a diversity of diseases, made it apparent that in diseases of the bone the serum phosphatase content becomes higher when there is extensive formation of abnormal bone or of osteoid tissue.

Josefsson<sup>51</sup>, studying 50 normal infants under 2 years of age, noted that tests made in the summer gave higher values than in the winter. The mean values for SAP by his original micromethod were 180, with the highest and lowest values being 310 and 90. In contrast, with 32 premature infants weighing from 1030 to 2830 gm., the SAP ranged from 110 to 620. More than half were

above the 300 reading. These higher SAP values did not correspond closely with the few signs of craniotabes and other evidences of rickets which were evident. The later development of the children did not show any relationship to the SAP levels. It was concluded that SAP determinations are without any real clinical value in the care of premature infants.

Vermehren<sup>94</sup> used an original micro-method to study SAP changes with ages. He too found somewhat lower values in the newborn period, with a rise at one month and an even greater rise at 2 months following which there was a slight decline to the first birthday and a further decline until 2 years of age. The values from then on were much the same from age 2 to age 10. In his scale the mean values for the newborn were 158, at 1 month 175, at 2 months 206, and 3 to 5 months above 235. The curves corresponding with increasing years ran identically for boys and girls until the 10th birthday. Above age 10 the girls showed slight elevation in the years age 10 to 13 years, while the boys had a slight drop at this time. Above age 13 the boys exhibited a rise whereas the girls in turn exhibited a drop.

Stearns and Warweg<sup>84</sup> have reported on the SAP values in 124 infants, children and young adults. The plasma content was low in the newborn, ranging from 0.1 to 0.2 (Kav method). At one month the mean unitage had risen to about the 0.5 level. At 4 and 6 months this was at the 0.3 level; at 12 months it was 0.25 and at 4 years it had fallen to 0.2 where it stayed essentially constant, until age 15 when it began to sink slowly to the adult level of slightly over 0.1. These figures were gathered from exclusively healthy children.

Tuba, Cantor, Siemens and Capsey<sup>92</sup> have reported on the findings of SAP among 108 school children aged 12 to

14 years in the neighborhood of Edmonton, Canada. Using a micromethod, important variations were found in SAP as related to sex, age groups, and season. For both children and adults the values for male subjects were appreciably higher than for females. The activity of the SAP was approximately 3 times greater among children than in a comparable series of 101 adults. The mean values in the spring were slightly higher for the boys than in the fall (13.5 vs. 12.8), whereas for the girls the values were 4.1 in the spring and 9.4 in the fall. The figures for acid phosphatase on these same children were 0.61 for the boys and 0.56 for the girls, this test being done only in the spring. There was a coincident slight decline in the level of serum inorganic phosphorus in the spring as compared with the fall.

Harrison and associates<sup>46</sup> have determined the level of AP in blood from 377 children aged 2 to 18 years, of whom 107 were studied in both fall and spring. Preliminary analysis showed the variations between duplicate determinations to be usually less than 0.4 nitrophenol units by the method of Bessey, Lowrie and Brach. Day by day tests on a number of children showed marked constancy with only 15% exceeding the maximum differences in duplicate analyses. The SAP levels ranged from 1 to 17 units, with a mean of 6.3 units. Approximately 84% fell between 4 and 9 units. Whether the values below 3 or 4 units were indicative of poor nutritional status could not be determined. Significant differences were not demonstrated between fall and spring in the 3 groups of subjects studied at both seasons, nor did the levels change appreciably during a 6-week period of "nutritional conditioning" in a health camp. Values indicative of active rickets in infants were not observed but a number of children had activity greater than 8 nitrophenol units,

the arbitrary upper limit of normal suggested by Bessey. There is no evidence, however, that these mildly elevated values were in any sense related to disease states. The levels for boys and girls under the age of 10 years were similar. A group of children under 10 years of age who tended to be larger than others had mean SAP levels nearly 2 units higher than the others.

**ADOLESCENCE.** Differences between older boys and girls have been reported. Bessey (cited by Harrison<sup>46</sup>) determined SAP levels of over 1000 children of 11 to 18 years of age. He found that the values for the males reached the peak at about 14 years of age and then dropped, whereas the values for girls at 11 years were already decreasing. Bessey commented that the SAP changes during puberty were difficult to correlate with other data such as the rate of bone growth or the rate of weight change. For example, the SAP values in boys were already dropping at 13 years, an age at which the rate of bone growth is still rapid. Harrison and associates are inclined to attribute the difference between teenage boys and girls to sexual maturation<sup>46</sup>. The maximum average level in girls occurs approximately at adolescence, and then drops to the levels characteristic of the adult. The average for the boys drops much less rapidly, and many have high values through the seventeenth year.

**Bone Diseases.** Elevated values for SAP are generally recognized as associated with some disturbance of either the bones or the liver. Increases are often seen in bone diseases which involve formation of new bone tissue<sup>50</sup>. Among these are hyperparathyroidism, osteogenic sarcoma, Paget's disease, osteomalacia, and osteosclerosis fragilis generalisata (marble bones)<sup>23</sup>. Essentially normal findings are obtained in most cases of osteomyelitis, bone cysts,

achondroplasia, cretinism, and calcinosis universalis. Slight increases have been occasionally noted in cases of renal rickets.

One of the earliest workers to point out that the SAP is elevated in rickets was Smith<sup>83</sup> in 1933. Using Kay's method the plasma phosphatase in 60 infants with radiologic evidence of rickets ranged from 0.41 to 1.29 units with an average of 0.772 units. (Control normal infants had a range of 0.2 to 0.3 units.) Smith also noted that of 15 infants having various conditions associated with cessation of growth, including scurvy, marasmus and celiac disease, the SAP values were not elevated.

Stearns and Warweg<sup>84</sup> followed the SAP levels of 3 older children with late rickets. One was 3 years of age; the second, 12 years; the third, 12 years. The values for plasma phosphatase were elevated at first and decreased slowly with vitamin D therapy, though were probably still well above normal when roentgenologic healing was complete.

Bodansky and Jaffe<sup>17</sup> found the SAP to range between 20 and 190 units per 100 cc. in 21 children with rickets of varying degrees of severity. The values were highest in very marked rickets (58 to 190 units), less than 20 units in mild rickets, and normal in healed rickets. When vitamin D was given to cases of marked rickets the SAP level became stabilized in the high normal range and remained there for some months before dropping further. This was interpreted as indicating that the level remains elevated while active healing is in progress and does not drop to normal until bone reconstruction is complete.

The most careful study of the relationship between SAP and rickets was that of Klasmer<sup>57</sup>, who found the mean value of SAP in 320 healthy children between 6 months and 2½ years of age to be 9.4 units (Bodansky), with a

normal range of 5.6 to 15.0 units. Sex and age did not influence the results. Fifty-five similar infants with active rickets were studied; the SAP in this group was elevated in all but a few. In most of these the readings were above 20 units. Parallelism was pronounced between the severity of rickets and the increase of phosphatase activity. In 500 other children with miscellaneous conditions, including many who were apparently well, an increase in SAP was found in seventeen. Two of these had subclinical jaundice, and the third had severe bone decalcification. The 14 other children had increased SAP (mean: 16.8 units) but dubious clinical signs of rickets at the first examination. Subsequent studies indicated that these children were suffering from rickets. Clearcut acute swelling of the epiphyses was almost always accompanied by increased SAP. Indefinite changes in the epiphyses were usually not a sign of active rickets; the mean value for SAP in 36 such cases was 10.77 units and roentgenograms also showed no active rickets. "When increased phosphatase activity is present, with insufficient or completely lacking clinical indications of rickets, a roentgenogram or repeated determinations of the phosphatase activity would show rickets as the cause. The phosphatase activity of the serum remains high throughout the period of active rickets; the decrease to normal values coincides fairly well with clinical recovery, while increase values for phosphatase activity may precede the first clinical symptoms<sup>57</sup>." In Klasmer's hands, as with most other workers, the determination of serum phosphorus is much less reliable as a diagnostic sign of rickets.

Klasmer found an interesting variation in the mean value for SAP in relation to seasons of the year. The levels for the control groups of 320 healthy children and for 625 other children

with poor development showed values which were more than 1.5 units higher in the winter than in the fall. The values for spring and summer were intermediate between those for winter and fall. This was interpreted as indicating that the SAP level is an indirect test for vitamin D; that there is a climax of saturation with vitamin D at the end of summer and a relative lack during winter even in children without any signs of rickets. It may be commented in passing that studies on the incidence of rickets must always differentiate between active rickets and healed rickets. Klasmer has attempted this differentiation. Most other workers have not.

Barnes and Carpenter<sup>6</sup> have reported on 187 infants with clinical signs of rickets and histories of low or absent vitamin D intake. Using the criterion of 12.5 mg. phosphatase per cc. as top normal, they found that 65.2% of the infants with rickets had SAP values above this level. They noted also that the level tended to subside as treatment was given, the average time for reaching normal being about 2 months.

Yieh and Wissler<sup>102</sup>, using Bodansky's method, found the SAP in 17 children with severe rickets to range from 14.5 to 57 units, with a mean of 28.4. In 15 milder cases the range from 7.2 to 16 with a mean of 11.2. Interestingly, there were two children with fever and rickets in whom the phosphatase levels seemed displaced downward.

Barnes, Munks and Kaucher<sup>8</sup> investigated SAP as an indicator for recovery in rickets. They found 798 infants in the child welfare clinic of Detroit over a 6 year period who were considered possibly rachitic. Of these, 199 had an SAP level of 20 units or more, which was deemed to be sufficiently above normal to be indicative of rickets. Forty-eight of these infants were divided into groups according to phosphatase ranges and treated with

vitamin D in cod liver oil or tuna liver oil at dosage of 600, 900 and 2400 I. U. of vitamin D daily. Each of these liver oils at all 3 medication levels caused significant drops in SAP by the sixth week and all but one by the fourth week. When the various groups were later compared, no significant differences were found in the relative degree of SAP reduction during the first 6 weeks of treatment.

Josefsson<sup>51</sup> has recorded the response of SAP to the so-called "shock" or massive single dose therapy of rickets, employing an original micromethod. The SAP was raised in 3 children with severe rickets, in all but 1 of 8 children with moderate rickets and in only 5 of 26 children with mild rickets. Comparative studies with blood phosphorus indicated that the SAP is a better criterion for the presence of rickets than is the low blood phosphorus. Of 21 infants with increased SAP given the massive dose treatment, the values for SAP remained high for at least 12 to 14 days afterwards in all with true rickets and fell to normal within 10 days in the remainder. It was concluded that if the values continue high after treatment or fall at a slow rate the rickets is more severe.

Van Creveld and Mastenbroek<sup>93</sup> described studies on both acid and alkaline phosphatase in rickets following injections of one single dose of 500,000 international units of vitamin D<sub>3</sub> as treatment for rickets. In 3 infants followed serially from the beginning of treatment the SAP dropped from abnormal to normal levels or to top normal levels, whereas the acid phosphatase showed a rise which reached a maximum 3 to 5 months after the injection of vitamin D<sub>3</sub>. By the King-Armstrong method the peak values were 14, 10.1 and 12 units respectively, as compared to more normal values in these children of 3.8 to 4.2 units. The curves for the 2 sorts of phosphatase

did not run parallel. The blood phosphorus level was abnormally low in these children at the beginning but promptly rose to normal range. In none of these children was there abnormal or increased values for calcium, cholesterol or inorganic phosphorus after the injection of  $D_3$ .

Saggese, De Luca and Daffi<sup>78</sup> also reported on the effects of single large doses of vitamin D on recovery of rickets. Using the King-Armstrong method they noted elevated SAP in 39 infants aged 9 to 36 months with rickets. The range was from 22 to 28 in mild cases to 21 to 88 in the severe cases. Following the injection of 20,000 to 50,000 I. U. of vitamin  $D_2$  in a single dose the SAP declined by 1.5 to 27 units.

*Scurvy.* Schwachman and Gould<sup>79</sup> studied the SAP in 18 infants with "unequivocal" scurvy, aged 7 to 13 months. The average value of serum phosphatase on admission to the hospital was 3.2 Bodansky units with a range of 1.1 to 4.9 units, as compared with the mean value for normal infants of approximately 7.2 with a range from 4.5 to 12 units. A substantial rise in this low level became apparent within a week following the institution of vitamin C therapy, even though vitamin D was withheld for the time. The SAP after 7 to 29 days of treatment ranged from 8 to 19 units. The rise was greatest in the child with extensive subperiosteal hemorrhages.

*SAP in Nutritional Surveys.* Youmans and associates<sup>103</sup> have described the results of a nutritional survey of a rural population in middle Tennessee with respect to vitamin D and calcium status. Three of 224 white children and 8 of 178 colored children had SAP values above 12 units (Bodansky). There were 12 other children under 12 years of age who had SAP activity above 12 units. None of these had rickets. Only 2 were infants, the others

being 5 to 13 years of age. Seven came from 3 families. Only 1 had received any vitamin D supplement and that only for 6 weeks. It is suggested that an elevated SAP in children above 3 years of age reflects vitamin D or calcium deficiency, or both. A total of 66 children under 15 years of age in the white group, and 49 in the colored group, had Bodansky units in the range from 8.0 to 11.9. These figures were interpreted as being "normal" but it is not impossible that some of these values represent an increase above normal. Clinical and laboratory indications of calcium deficiency were uncommon. The incidence of diagnosed rickets, on the basis of the other criteria in this study—physical examination especially of the skeleton, signs of tetany, roentgenograms of some of the bones, and phosphatase, phosphorus and calcium concentrations in the blood—indicated that evidences of rickets were present in about 25% of the subjects under 3 years of age, though in many of these the disease was probably healed. What makes surveys for calcium or vitamin deficiency so difficult is that there are few symptoms and signs except in the relatively severe or advanced deficiency states. It is unfortunate that in this survey the phosphatase test was done with only a few of the younger subjects who had clinical signs of rickets.

In August 1944 a survey was made by Adamson and associates<sup>1</sup> of the nutritional status of the population of Newfoundland, especially in the city of St. John's and several nearby ports. The general conclusion was that the nutritional status of the people in general was poor, inasmuch as evidence of lack of vitamin A, riboflavin and ascorbic acid was seen with great frequency. Phosphatase studies were carried out on many of the individuals. Nearly all the values for both children and adults were within normal limits. With the method of Bessey, Lowrey and Brock<sup>11</sup>,

the mean level was 4.9 units for children under 18 years of age and 1.9 units for adults above 18 years of age. Only 4.9% of the children had values higher than 8 units taken as the top normal and only 1.9% of the adults were above 3 units which is the value of top normal for adults. It was concluded by the authors that these findings indicated, in general, an absence of vitamin D deficiency within the population.

*Hypothyroidism.* Talbot<sup>87</sup> applied the phosphatase test to the study of patients with hypothyroidism, following the observation by Bodansky and Jaffe<sup>17a</sup> that a girl cretin 4 years of age with a normal SAP showed a rise after thyroid treatment. The original levels for 4 out of 5 such untreated children were unusually low (average 3.0 Bodansky units). These children ranged in age from 3 months to 10 years. After several months of thyroid therapy the levels of SAP were restored to normal (average 8.5 Bodansky units).

Talbot and associates<sup>88,89</sup> later described the SAP values in 30 infants and children with cretinism and juvenile hypothyroidism. In 12 of these the levels were studied before thyroid therapy. The value for SAP was lower than 4.5 units per 100 cc. for 11 of these untreated patients and at 6.0 for the 12th patient. In contrast, these and other patients after receiving thyroid therapy had SAP values coinciding with the normal range (Bodansky). The values later diminished again when thyroid therapy was reduced or discontinued. Lower levels of SAP were not observed in diseases which might be confused with juvenile hypothyroidism or cretinism, with a possible exception of a few cases of idiopathic dwarfism. The average value for SAP in 8 children with idiopathic dwarfism was 6.6 units (range 4.5 to 9.0 units). Mention is made of the fact that in some cases of scurvy, severe malnutrition,

severe anemia, arthritis, achondroplasia, splenomegaly and abdominal tumors there may be a lowering of the SAP. Bixby<sup>13,14</sup> concluded that the levels of SAP were normal in mongolism. Talbot<sup>89</sup> concludes that SAP is useful as an index of thyroid function in children, provided the other diseases which may cause a lowering of SAP are excluded.

Hill and Weber<sup>18</sup> have reported on studies of 23 children showing obvious retardation in development and low basal metabolic rate due presumably to hypothyroidism. The children ranged in age from the newborn period to 13 years. These 23 children showed symptoms of mild hypometabolism clinically, and, in addition, either marked osseous retardation or low metabolic rates. Twenty of the 23 children had SAP values of 5.6 Bodansky units or less. The 3 others had values between 6.4 and 6.8 units. In 14 out of 16 control children the range was 5 to 9.7 units. Two children with normal osseous development and low SAP had minor symptoms suggestive of hypothyroidism. After receiving thyroid therapy for one month as a therapeutic test, they showed clinical improvement along with increased values of SAP approaching the normal range. Hill and Weber conclude that as much or more information can be derived from the SAP determination than from the serum or plasma cholesterol tolerance test in mild hypothyroidism. The chief advantage to the SAP test is its comparative simplicity and lack of expense.

*Liver Disease.* In adult patients with jaundice it is often thought that complete obstruction of the common bile duct is usually associated with a marked increase in SAP, whereas hepatitis may or may not induce such an increase. The fact that adults with incomplete obstruction may exhibit an increased SAP without any increase of serum bilirubin is attributed to less efficient



permeability of the kidney to phosphatase as compared with permeability to bilirubin<sup>44</sup>.

Rapoport<sup>73</sup> has presented observations on 15 children on whom determinations of phosphatase, along with other tests of liver function, were obtained in the early stages of infectious hepatitis. There were 13 children, ranging in age from 7 to 14 years. Eight of the children were examined the day after the jaundice was first noted, and the others within the first week of jaundice. One of these was diagnosed as having hepatitis without jaundice. Each child showed a slight elevation in the SAP at the time of first testing, the values ranging from 14 to 37 units (Bodansky). These elevations were transient, and as a rule fell to normal within a week. There was no appreciable parallel between the rise in SAP and the rise in serum bilirubin. This was interpreted as indicating that a rise in SAP during hepatitis reflects a stimulation in the formative activity of the liver rather than a suppression of its excretory activity. The author suggests that the more frequent incidence of increased SAP in obstructive jaundice may be due, at least in part, to a stimulation by biliary obstruction upon formation of phosphatase by the liver cells. Reference is made to the observation by several workers that infants with congenital atresia of the bile ducts may have only a moderately increased SAP, if any at all. Rapoport suggests that in such patients, if the "retention" theory be correct, high levels of SAP would obtain. The fact that there is no appreciable increase indicates that the element of retention, at least in this type of obstructive jaundice, plays only a minor role.

Payne comments that in 54 children with jaundice, usually of the infectious type, the SAP was often elevated, especially in the early stages<sup>71</sup>. There was no parallelism between the SAP and

bilirubin level or the clinical course. While it is difficult to draw many conclusions from a single test of SAP, Payne suggests that children with mild infectious hepatitis should not be regarded as cured if the phosphatase has not yet returned to normal.

Gall's observations in infectious mononucleosis may be mentioned in this connection<sup>36</sup>. Gall performed SAP tests on 34 patients with infectious mononucleosis (all adults) and found significant elevation in all but one instance. The readings ranged from 8 to 44 Bodansky units (top normal for adults: 4 units). This elevation was attributed to altered liver function, the reasons being that anatomic lesions have been found in the liver in the rare case of infectious mononucleosis available for such study and abnormal results were also shown in other liver function tests carried out with these same patients.

MISCELLANEOUS. SAP has been found to be elevated in a case of epiphyseal dysgenesis<sup>15</sup>. Yieh and Wissler<sup>102</sup> found SAP to be normal in children with renal rickets and hyperphosphatemia whereas it was raised in the hypophosphatemic form of the Fanconi syndrome. This was substantiated by McCune<sup>66</sup> and workers who found an elevated SAP in a case of intractable hypophosphatemic rickets. Gill<sup>37</sup> has reported studies on 3 children and 1 adult with vitamin resistant rickets. The 3 children all had markedly elevated SAP whereas the adult who was the mother of 2 of the children had normal SAP. Gunther<sup>43</sup> found that the SAP was normal or slightly elevated in a case of rickets resistant to vitamin D therapy but increased sharply on administration of higher doses of vitamin D. SAP was normal in multiple cystic tuberculosis of the bone<sup>64</sup> and depressed in osteopetrosis<sup>26</sup>, osteochondrodystrophy deformans<sup>30</sup> and in a peculiar osseous disease characterized



by areas of increased bone density and dilatation of the bone shaft<sup>76</sup>.

SAP has been found depressed in a case of progeria<sup>89</sup> and in the post-acidotic state of infantile diarrhea<sup>74</sup>. Of 11 children with celiac and celiac-like disease, 7 had subnormal values, 1 with a reading of 2.2 units<sup>102</sup>. One child with uremic vomiting gave a reading of only 2.4 units<sup>102</sup>. It was normal in both diabetic<sup>97</sup> and pituitary dwarfism<sup>21</sup>.

Mason and Henderson<sup>65</sup> found a normal SAP in a case of glycogen storage disease. Another case of glycogen storage disease was reported to have a reading of 15.4 units on one occasion and later 2.4 units<sup>102</sup>. In 2 children with osseous dystrophy following icterus gravis neonatorum, Braid<sup>19</sup> noted increased SAP in association with the bone changes and evidence of liver dysfunction. In these cases the bone dystrophy was ascribed to the failure of the liver to store and utilize vitamins.

Of 6 patients with anemias of various sorts (1 with Cooley's anemia), 4 had subnormal values (2.0 units or less) and 2 others had low normal values (4.0 to 4.8 units)<sup>102</sup>.

CONGENITAL "HYPOPHOSPHATASIA." Rathbun<sup>74a</sup> has described the extraordinary case of a deformed newborn infant whose bones exhibited lack of calcification and marked epiphyseal enlargement, along with almost absent SAP during life and comparatively negligible amounts of extractable AP in the bones and other tissues after death at the age of 2 months. The vault of the skull was almost devoid of calcium. The low to absent AP was believed to be the primary defect responsible for the clinical picture and the coined term "hypophosphatasia" was applied to it. The case report gives no information with respect to the acid phosphatase content of blood and tissues or to any histologic studies with special stains for the phosphatases.

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PHYSIOLOGY  
PROCEEDINGS OF  
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA  
SESSION OF MARCH 15, 1949

The Effects of Jet Engine Noise on the Cochlear Response of the Guinea Pig. IRVING E. ALEXANDER, Ph.D., and FREDERICK J. GITHLER, A.B. (Dept. of Psychology, Princeton Univ.). This work was carried out in the Princeton Psychological Laboratory, with the co-operation of the Naval Air Experimental Station, Aeronautical Medical Equipment Laboratory, Captain J. R. Poppen, M. C., commanding, under contract with the Office of Naval Research, as Contract N6-onr-270, Task Order III (Project NR 145-322) and Bureau of Medicine and Surgery, NM 003-037. Cochlear potentials were measured at various time intervals for 4 groups of guinea pigs after a 15 minute exposure to jet engine noise. A control (non-exposed) group was also tested. The findings are as follows: 1, Exposure to the jet engine noise results in auditory impairment throughout the frequency range. 2, Partial recovery occurs progressively up to 3 weeks following the exposure. 3, After injury, the cochlear potentials are further impaired on the presentation of even moderately intense sounds. The exposed ear has been rendered unusually susceptible to further injury. 4, There is preliminary evidence that indicates the possibility that further degeneration occurs between 3 and 6 weeks after jet stimulation. 5, Results based on a limited sample disclose that protected ears show no immediate effects in auditory acuity. However, after a period of 6 weeks some deterioration is observed.

Tentative explanations of the results are offered, and recommendations are made for concerned personnel.

Simultaneous Comparisons of Alveolar Gas Tensions Obtained by Various Sampling Methods. E. S. BARKER, M.D., R. G. PONTIUS, M.D., D. M. AVIADO, M.D., and C. J. LAMBERTSEN, M.D. (Dept. of Pharmacology, Univ. of Penna.).  $PO_2$  and  $pCO_2$  of alveolar gas was determined for samples obtained simultaneously by various methods: 1, Haldane-Priestley end-expiratory; 2, Rahn (continuous, end-normal expiratory, from beyond mouth); 3, Tracheal (continuous, end-normal expiratory, from a catheter introduced through the crico-thyroid membrane to the tracheal bifurcation); 4, "Effective" method of Riley *et al.* (calculation based on expired gas, blood  $pCO_2$  and expired gas R.Q.); 5, Alveolar Equation of Bohr (calculation by correcting expired gas for the effect of the dead space. Several representative dead space values were used). Expired gas was collected in a Tissot gasometer. All gas samples were analyzed with the Scholander .5 cc. gas analyzer. Gas tensions of arterial blood, collected simultaneously and analyzed by a direct microtonometric method (modified after Riley *et al.*), were compared with the alveolar tensions.

Measurements were made on 11 resting, normal, young, adult males. Samples were collected during 3 experimental periods of 2 minutes on each subject. The state of relaxation was observed by the constancy of alveolar  $pO_2$  determined with a Pauling tensimeter by the Rahn method. The results are summarized in Table 1.

The variability for each method due to variation between different individ-

uals and that due to repeated measurements on the same individual has been determined statistically.

An analysis was made of the statistical differences between individual measurements obtained by the various methods. For  $pO_2$  there was a statistically significant difference between all comparisons except: 1, Haldane-Priestley and arterial blood; 2, Effective and Haldane-Priestley; and 3, Effective and Tracheal (these 2 show the smallest difference).

For  $pCO_2$  there were no statistically significant differences except that the Rahn differed from each of the other values. (Since they are not independent

duced as a means of evaluating other methods. Although no serious difficulties were encountered, the method is not considered practical for routine use.

**Isotopic Studies of the Biosynthesis of Nucleic Acid Components. I. Purines and Pyrimidines.** MILTON R. HEINRICH\*, Ph.D., D. WRIGHT WILSON, Ph.D., and SAMUEL GURIN, Ph.D. (Dept. of Physiological Chemistry, School of Medicine, Univ. of Penna.). Carbon dioxide, acetic acid, and glycine have been studied as possible precursors of the nitrogenous bases of nucleic acids and nucleotides in the rat. The

TABLE 1.—ALVEOLAR AND ARTERIAL GAS TENSIONS

Sample or Method	$pO_2$		$pCO_2$	
	Mean	Std. Dev.	Mean	Std. Dev.
Arterial Blood	96.6	$\pm 4.1$	40.5	$\pm 4.4$
Haldane-Priestley. End-Expiratory	98.0	$\pm 5.6$	40.6	$\pm 3.2$
End-Inspiratory	104.3*	$\pm 5.7$	38.7*	$\pm 3.5$
Mean	101.2*	$\pm 5.7$	39.7*	$\pm 3.8$
Rahn <i>et al.</i>	103.1	$\pm 4.1$	38.6	$\pm 2.4$
Tracheal	99.7	$\pm 3.9$	40.4	$\pm 2.9$
Effective (Riley <i>et al.</i> )	100.3	$\pm 5.5$	40.5**	$\pm 4.4$
Alveolar Equation. D.S.=.3 X Tidal Vol.	99.6	$\pm 4.1$	42.0	$\pm 3.4$
D.S.=150 cc.	97.6	$\pm 7.1$	43.3	$\pm 5.1$
D.S.=180 cc.	91.8	$\pm 10.6$	48.2	$\pm 7.4$

\* From a later series (25 measurements on 13 normal resting men).

\*\* Effective  $pCO_2$  is assumed to equal arterial blood  $pCO_2$ .

values, the alveolar equation calculations were not included in these comparisons.)

The significant difference between the Rahn and the Tracheal, although both were measured simultaneously at the same phase of respiration, suggests that an ordinary normal expiration is not sufficient to wash out the dead space.

The fact that the Tracheal and the Effective methods show the closest correlation and that these 2 methods are entirely independent is indirect evidence in favor of values obtained by these methods.

The Tracheal method was intro-

duced as a means of evaluating other compounds, labeled with radioactive carbon, were administered to rats, followed by isolation of the purines and pyrimidines from the tissues, and assay of their radioactivity. Nucleotides were first extracted from the carcasses with cold trichloroacetic acid, hydrolyzed and adenine isolated. After removing lipids from the remaining tissue, the nucleic acids were extracted with hot 10% sodium chloride, and hydrolyzed to individual purines and pyrimidines.

After hourly injections of labeled  $NaHCO_3$  into a rat for 7 hours, a small amount of isotope was found in the adenine of the nucleotides and in the adenine, guanine and uracil of nucleic

\* National Institutes of Health Postdoctoral Research Fellow.

acids. The isotope was shown by means of permanganate degradations to be in the non-ureide carbon of guanine and the ureide carbon of uracil. Carboxyl-labeled sodium acetate, injected into rats for 5 days, gave approximately the same degree of incorporation; no isotope appeared in the ureide or guanidino carbons of guanine.

Excellent incorporation into the purines was observed when glycine labeled in the carboxyl group was fed to rats for 10 days. The isotope concentration was approximately equal in nucleic acid, guanine and adenine, and slightly higher in nucleotide adenine. To determine the position of the isotope in the nucleic acid guanine, a sample was hydrolyzed with concentrated HCl at 200° to give glycine in which the carboxyl carbon is known to be derived from carbon 4 of guanine. The carboxyl of this glycine, obtained as CO<sub>2</sub> by treatment with ninhydrin, contained essentially all the isotope present in the guanine.

**Nucleic Acids and Antibody Production by Plasma Cells.** CAROLYN FORMAN, M.D., D. L. DRABKIN, M.D., and W. E. EIMICH, M.D. (Depts. of Pathology and Physiological Chemistry, Grad. School of Medicine, Univ. of Penna., and the Phila. General Hospital.) Rabbits were injected with typhoid antigen into each foot pad, and the formation of antibody was compared with the changes in nucleic acids in the popliteal lymph nodes. Desoxyribose nucleic acid (DNA) and ribose nucleic acid (PNA) were determined by the method of Schneider as adapted by Drabkin. Sections of the nodes were stained with methyl green and pyronin.

It was found that DNA increased immediately with the weight of the node, whereas the peak of PNA increase occurred between the 4th and 6th day after vaccine injection when antibody formation is at its maximum.

A study of sections revealed that during the first 6 days of the experiment the cellular reaction was chiefly that of plasma cells. Most of the PNA was contained in the plasma cells. The lymphocytes began to proliferate in significant numbers on the 3rd and 4th day, and germinal centers began to appear on the 4th and 5th day. They showed their greatest activity on the 9th day when PNA and antibody formation had passed their peaks. These results are interpreted as indicating that the plasma cell and not the lymphocyte are responsible for antibody formation.

**The Standardization of Hemoglobin Measurement.** DAVID L. DRABKIN. (Dept. of Physiological Chemistry, Grad. School of Medicine, Univ. of Penna.). A simplified, reliable procedure for the standardization of hemoglobin measurement, with hemoglobin iron as the ultimate basis of reference, has long been needed. There is now convincing evidence that the spectrophotometric or photometric determination of cyanmethemoglobin, MHbCN, is the most direct analysis available for total hemin or hemoglobin iron<sup>1</sup>. Tedious and exacting standardization procedures may be circumvented in the calibration of commonly used photoelectric filter photometers for the accurate measurement of hemoglobin concentration. This is done by employing established ratios of optical density,  $D$ , at a suitable wave-length (green spectral region; filters with maximum transmittancy at 540 m $\mu$  and at specified concentrations, for MHbCN or for oxyhemoglobin, HbO<sub>2</sub>, and a standard solution of cupric ammonium sulfate, Cu, prepared gravimetrically and volumetrically<sup>2</sup> from a good grade of commercial cupric sulfate, CuSO<sub>4</sub> · 5H<sub>2</sub>O. Such calibration ratios or factors are:  $D_{\text{MHbCN}}/D_{\text{Cu}} = 1.020$ ,  $D_{\text{HbO}_2}/D_{\text{Cu}} = 0.963$  (applicable to the Klett-Summer-

son photometer), and 0.857 and 0.890, respectively (applicable to the Evelyn instrument). The factors were established for hemoglobin at a concentration of 0.0358 mM/L (0.0598 gm./100 ml., *i. e.*, blood, originally containing exactly 15.0 gm. of hemoglobin per 100 ml., diluted 1:251) and for the copper standard at a concentration of 0.012 M/L. An example of the use of the ratios follows: in a Klett-Summerson photometer, the copper standard yields  $\underline{D}_{Cu} = 206$ . On this instrument, a blood sample, originally containing exactly 15.0 gm. of hemoglobin per 100 ml., diluted 1:251 (and converted to MHbCN), would give the value 210 for  $\underline{D}_{MHbCN}$  (from  $\underline{D}_{Cu} \times$  established factor, or  $2.06 \times 1.020$ ). This simple procedure effectively calibrates the instrument for hemoglobin measurement.

It has appeared desirable to go a step beyond this procedure, and provide a relatively permanent glass standard. For this purpose a stable, Corning blue glass filter,  $\underline{f}$ , No. 4305, 4.2 mm. thick, cut into appropriate size and shape, and suitably mounted in metal jackets for adaptation to the

Klett-Summerson or Evelyn instruments, has been employed. For these particular filters, as an example,  $\underline{D}_{Cu}/\underline{D}_f = 1.190$ .  $\underline{D}_{Cu}/\underline{D}_f$  is, of course, obtained from the determined values of the copper standard and standard glass filter for each instrument. In this case,  $\underline{D}_{Cu} = 206$ ,  $\underline{D}_f = 173$ , and, hence,  $\underline{D}_{Cu}/\underline{D}_f = 1.190$ . Now, since the established factor,  $\underline{D}_{MHbCN}/\underline{D}_{Cu} = 1.020$ ,  $\underline{D}_{MHbCN}/\underline{D}_f$  must equal  $1.020 \times 1.190$ , or 1.214.

In using a new glass filter, it must either be pre-calibrated, *i. e.*, the  $\underline{D}_{MHbCN}/\underline{D}_f$  or  $\underline{D}_{HbO_2}/\underline{D}_f$  ratios must be furnished, or the glass must be calibrated against the copper standard, as above, and the hemoglobin to glass factor obtained from the established ratios of  $\underline{D}_{MHbCN}/\underline{D}_{Cu}$  or  $\underline{D}_{HbO_2}/\underline{D}_{Cu}$ . Both the copper solution and calibrated glass serve as desirable instrumental performance standards, to be used periodically, as well as for the calibration of the instrument for hemoglobin measurement. The same method has broad photometric applicability, and may be suggested for many other methods, besides hemoglobin.

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# BOOK REVIEWS AND NOTICES

**ACCLIMATIZATION IN THE ANDES. HISTORICAL CONFIRMATION OF "CLIMATIC AGGRESSION" IN THE DEVELOPMENT OF ANDEAN MAN.** BY CARLOS MONGE, M.D., Univ. of San Marcos, Lima. Translated by Donald F. Brown, Ph.D. Introduction by ISALAH BOWMAN, Johns Hopkins Univ. Pp. 130. Balt.: Johns Hopkins Press, 1948. Price, \$2.75.

THE content of this small book is well expressed in its subtitle. The author, a scientific physician and former Dean of the Medical Faculty at Lima, has for many years studied "climatic aggression" (i.e., the effects of "air temper") on Peruvian coastal dwellers and Andean uplanders. (The word "air-temper" is a valuable adaptation of the "temple" of the old Spanish chroniclers, used to indicate the general state of the air-temperature, humidity, atmospheric pressure, etc.) The author makes a vigorous plea for the use of the knowledge gained to improve the physical condition of Peruvians. E. K.

**PRACTICAL ASPECTS OF THYROID DISEASE.** BY GEORGE CRILE, JR., M.D., Cleveland Clinic. Pp. 355; 101 ills. Phila.: W. B. Saunders, 1949. Price, \$6.00.

DRAWING from his experience in the surgical treatment of approximately 1000 patients with diseases of the thyroid, the author presents a concise, lucid treatise on thyroid disease. The mode of action and present status of the anti-thyroid drugs in the treatment of hyperthyroidism is discussed and there is a detailed account of the preoperative and postoperative care and technique of thyroidectomy. A large section of the monograph is devoted to malignant tumors of the thyroid.

Owing to controversial opinions currently existing, the author's views relating to such problems as the use of the anti-thyroids in the treatment of hyperthyroidism, the value of radioactive iodine, and the treatment of cancer of the thyroid may not be generally acceptable, but he acknowledges the fact that sufficient time has not yet elapsed to evaluate completely the newer forms of therapy. The importance of having a team of specialists skilled in surgery, internal medicine, Roentgen therapy, and nuclear physics in studying thyroid disease is stressed. I.R.

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## NEW BOOKS

*Nursing of the Sick—1893.* By ISABEL A. HAMPTON and Others. Pp. 218. New York: McGraw-Hill, 1949. Price, \$3.50.

*Neurological and Neurosurgical Nursing.* By C. G. DE GUTIERREZ-MAHONEY, M.D., Assoc. Prof. of Neurology, Vanderbilt Univ. School of Medicine, and ESTA CARINI, R.N., B.S., Neurological Inst., Presbyterian-Columbia Medical Center, New York. Pp. 516; 51 ills. St. Louis: C. V. Mosby, 1949. Price, \$5.75.

*Thyroid Function as Disclosed by Newer Methods of Study.* Edited by J. H. MEANS, and 12 Others. Pp. 229; illustrated. Ann. New York Acad. Sci., 50, 279-508, 1949. Price, \$3.00.

*Safer Ways in Nursing.* By JOINT TUBERCULOSIS NURSING ADVISORY SERVICE. Pp. 108. New York: National Tuberculosis Assoc., 1948. Price not given.

*British Encyclopaedia of Medical Practice. Medical Progress, 1949.* Edited by Rt. Hon. LORD HORDER, Physician to the King. Pp. 431. London: Butterworth & Co., Ltd., 1949. Price not given.

As in earlier volumes, *Medical Progress* is treated under Critical Surveys (121 pages covering 12 fields of medicine): Drugs, the *British Pharmacopoeia* 1948 (17 pages) and Abstracts, ranging from Abdominal Pain through Whooping Cough (250 pages).

*Medical Clinics of North America.* National Number. Pp. 313; 30 ills. Philadelphia: W. B. Saunders, March, 1949. Price, \$15 a year.

This volume presents a symposium on treatment of long-term illness. It discusses such subjects as hypertension, vascular diseases, heart failure, tuberculosis, non-tuberculous lung diseases, asthma, diabetes, blood dyscrasias and other chronic problems. Most of the presentations avoid quoting experimental work and confine themselves to practical clinical discussions. There are excellent articles on Chronic Illness and the Constitutionally Inadequate, Mastery of Long-Term Illness, Planning for Long-Term Illness and The Patient with Long-Term Illness as a Surgical Risk. This volume maintains the high standards of this series. H. H.

*Introduction to the Szondi Test.* By SUSAN DEU. Foreword by DR. LIPOT SZONDI. Pp. 354; 19 figs. New York: Grune & Stratton, 1949. Price, \$5.00.

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